ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

Editorial
Myocardial Oxygen Demand vs Oxygen Supply

Cardiovascular Anesthesia
Human Coronary Artery Dilation and Isoflurane vs Halothane
Porcine Coronary Artery Dilation and Isoflurane vs Halothane
Intrarenal Cross-Clamp-Induced Renal Impairment

Neurosurgical Anesthesia
Hydroxyethyl Starch and Coagulation
Fentanyl and the Blood-Brain Barrier

Ambulatory Anesthesia
Rocuronium and Endotracheal Intubation
Intraoperative Patient-Controlled Analgesia

Pediatric Anesthesia
Colorimetric End-Tidal CO_2 Detection in Children
Oral Midazolam and Adjuncts in Children

Obstetric Anesthesia
Vasopressor, Epidurals, and Cesarean Section
Epidural Morphine and IM Diclofenac for Postcesarean Analgesia

Regional Anesthesia and Pain Management
Clonidine, Epinephrine, and Brachial Plexus Block
R(+)- and S(−)-Mepivacaine Pharmacokinetics in Humans
Phenobarbital and Experimental Pain
Flumazenil and Lidocaine-Induced Seizures

Original Articles
Preoperative Anxiety and Gastric Volume-Acidity
Omeprazole vs Ranitidine and Gastric pH
Ketorolac, MAC and Ventilation in Rats
Chloride Transport and Halothane MAC
Anesthesia and Unconscious Learning
O_2 Consumption and CO_2 Elimination During Inflation of Leg Tourniquet
HIV Risk in Medical Personnel

ISSN 0003-2999 Volume 75, Number 1, July 1992

For long surgical procedures...

ARDUAN

(pipecuronium bromide

for injection

Long-acting muscle relaxation without vagolytic effects[1]

- Does not cause elevation of heart rate or blood pressure.[2]
- Histamine-related reactions are unlikely to occur.
- Recommended when cardiovascular stability is desired.[3]
- A useful alternative to pancuronium in patients where tachycardia is best avoided.[4]
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

© 1992 ORGANON INC.

ORG-13639 PRINTED IN USA JANUARY 19

ARDUAN®
(pipecuronium bromide)
for injection

P, 24, 539

CVE-H02996-48-P024539

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.

WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.

PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.

Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, e.g., slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dosage should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.

Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.

Long-Term Uses in the Intensive Care Unit (ICU): No data are available on the long-term use of ARDUAN® in patients undergoing mechanical ventilation in the I.C.U.

Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.

Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. Since the neuromuscular blocking agents are routinely administered before or shortly after the administration of the inhalation anesthetic, minimal effects are generally observed on onset time and peak effect. In routine use of neuromuscular blocking agents, only clinical duration is generally affected (prolonged). No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with ARDUAN® during surgery, prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by hypokalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (e.g., diarrhea) or chronic (e.g., adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (Caesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following Caesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (C-section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.

Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:

Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult intubation.

Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, urticaria.

Urogenital system: anuria.

HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36).

Storage: 2°-30°C (35°-86°F). Protect from light.

After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

CAUTION: Federal law prohibits dispensing without prescription.

Rev. 12/91

REFERENCES

1. Data on file.
2. Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Can J Anaesth.* 1990;37(5): 549-555.
3. Larijani GE, Bartkowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. *Anesth Analg.* 1989;68:734-739.
4. Tassonyi E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology.* 1988;69(5):793-796.

Manufactured by
ORGANON INC. WEST ORANGE, NEW JERSEY 07052

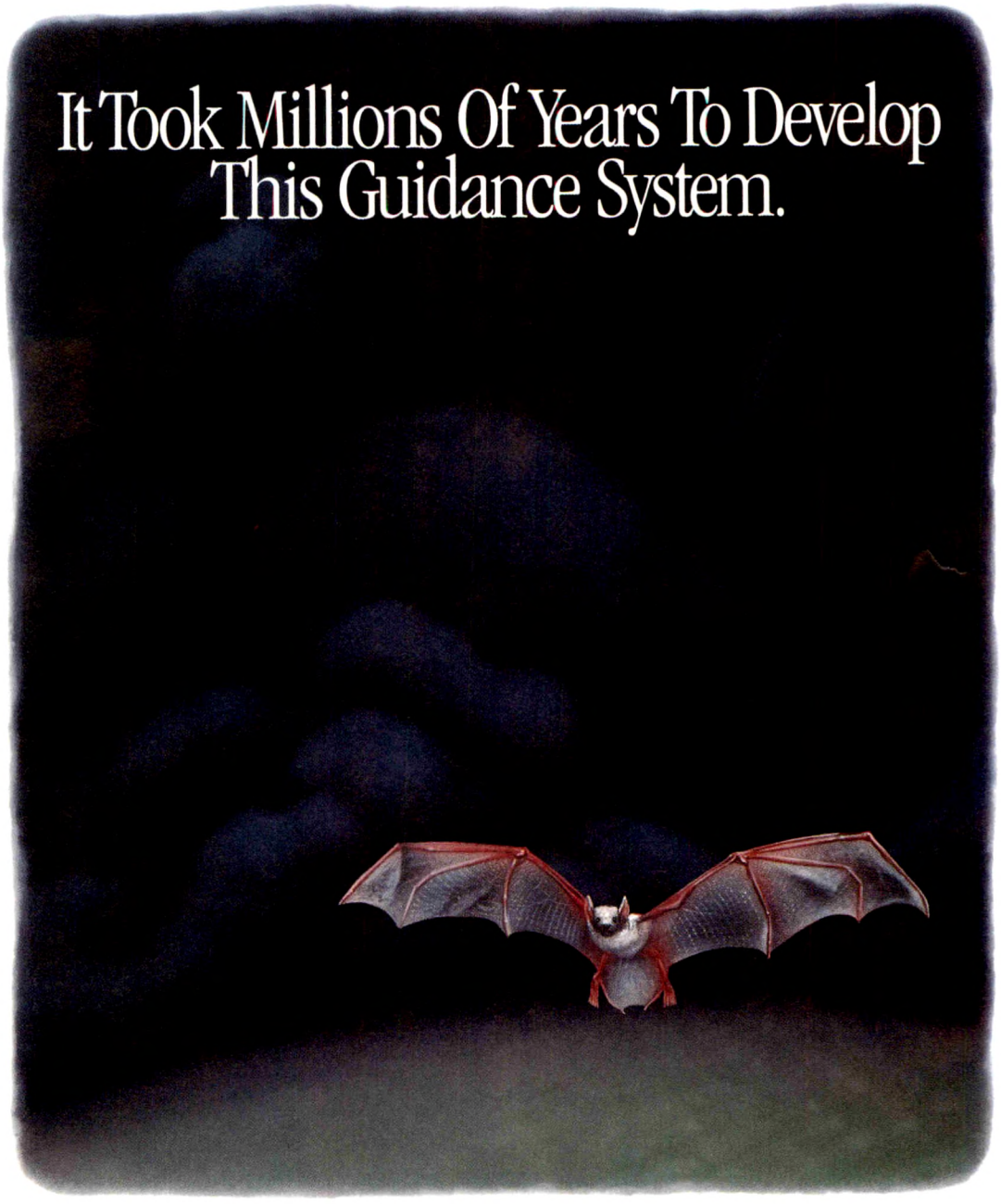
or by

BEN VENUE LABS., INC. BEDFORD, OHIO 44146
PTD IN USA 446 1/92

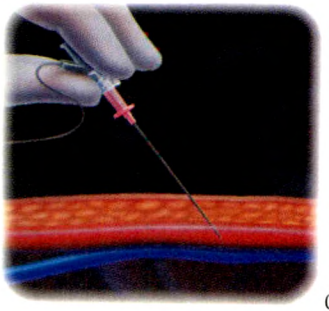
Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

"® Registered Trademark; Licensed from the chemical works of Gedeon Richtor, Ltd., Budapest, Hungary"


It Took Millions Of Years To Develop
This Guidance System.

You'll Appreciate Its Accuracy In Seconds.



Only SmartNeedle guides your needle straight to its mark with the speed of sound.

Whether your target is a femoral, subclavian or internal jugular vessel, you'll be able to distinguish arteries from veins by the sounds SmartNeedle transmits.

Continuous auditory feedback helps you locate the vessel with pinpoint accuracy, puncture it and optimize the needle position within the vessel.

Proven Doppler technology helps your needle find its target while minimizing trauma and complications associated with multiple punctures. Therefore, less time is spent in preparation and patient care can begin without unnecessary delay.



It's easy to see, and hear, why SmartNeedle is essential in the OR, ER, ICU, specials and cath labs. And using it is as easy as it sounds.

What's more, our dedicated service and support are your assurance that it will always be a device you can rely on.

Call 1-800-548-1994 today for more information or to request a demonstration. And get your hands on the technological alternative to flying blind.

***Smart*Needle™**

Pinpoint Accuracy With The Speed Of Sound.™

PG® Peripheral Systems Group

A Division of ACS® 1395 Charleston Rd., Mountain View, CA 94043

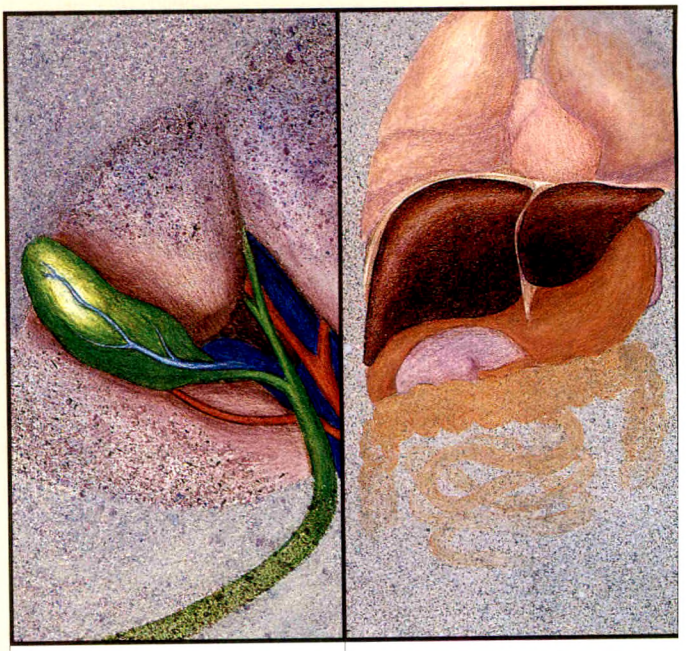
SmartNeedle is a registered trademark of Peripheral Systems Group.

SmartNeedle Vascular Access Guidance System designed in conjunction with Paul G. Yock, M.D. This product is intended for use by or under the direction of a physician. Prior to use, it is important to read the package insert thoroughly for instructions on use, warnings and potential complications associated with the use of this device. Manufactured under the following patent: United States, 4,887,606. Other U.S. and foreign patents pending. ©1992 Peripheral Systems Group

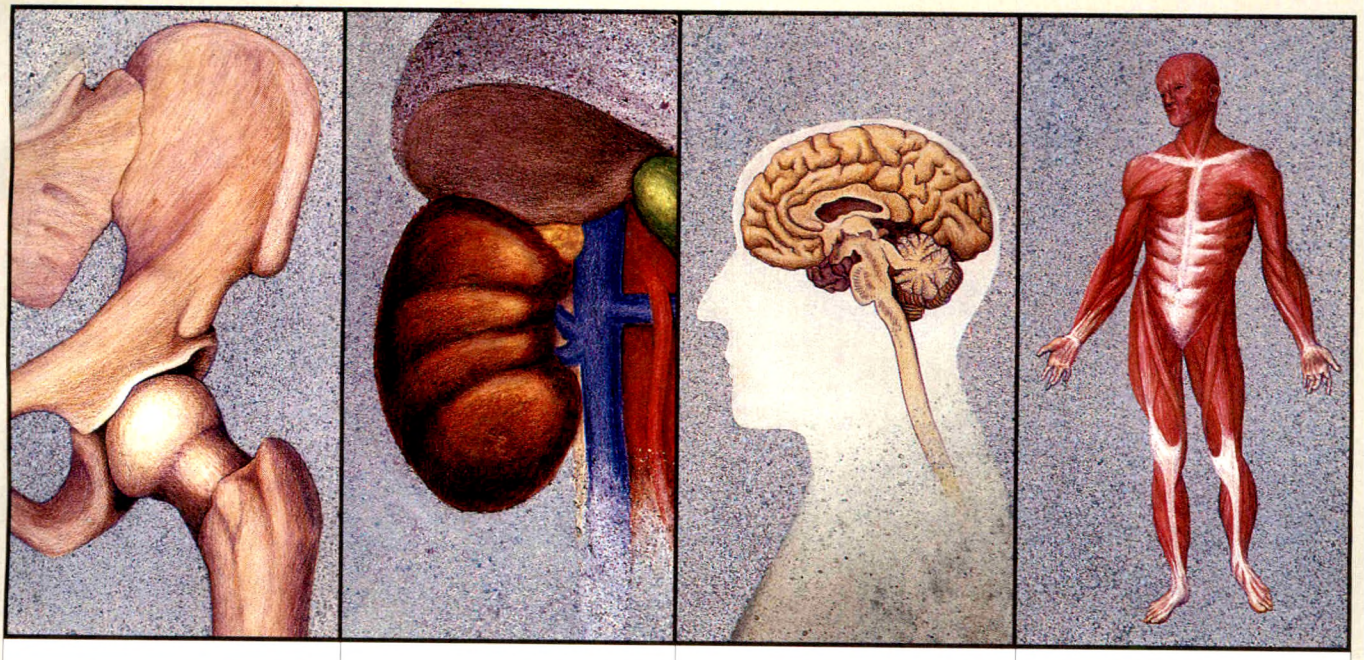
Tracrium®

For many procedures

For many reasons



Cholecystectomy	Biliary tract repair
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]



Total hip replacement	Renal surgery	Neurosurgery for trauma	Everyday procedures
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM® *INJECTION*

(atracurium besylate) 10 mg/mL

For pr dictabl r cov ry

TR-Y03368

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/675 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67:1149-1153. 2. Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172. 3. d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology.* 1983;59:237-240. 4. Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology.* 1985;63:A331. Abstract. 5. Ebrahim Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg.* 1988;67:S55. Abstract.

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Copr. © 1991 Burroughs Wellcome Co. All rights reserved.

TR-Y03368

DEPARTMENT OF ANAESTHESIA
HARVARD MEDICAL SCHOOL

From time to time, positions are available in the Anaesthesia Departments of several hospitals affiliated with Harvard Medical School in the residency, fellowship, faculty, and technical ranks. These hospitals include: Beth Israel Hospital; Brigham and Womens' Hospital; Cambridge Hospital; Children's Hospital; Massachusetts Eye & Ear Infirmary; Massachusetts General Hospital; Mount Auburn Hospital; New England Deaconess Hospital; and West Roxbury Veterans Administration Hospital. Interested individuals should apply directly to

Richard J. Kitz, M.D.
Secretary of the Department of Anaesthesia
Massachusetts General Hospital
Boston, MA 02114

Applications are also invited from Board-certified or eligible physician anesthetists for two or three year research fellowships in the laboratories of Harvard University, Massachusetts Institute of Technology, Massachusetts General Hospital, Beth Israel Hospital, Brigham and Womens Hospital and Childrens Hospital. Appointments are made annually under USPHS National Research Service Award for advanced training in the Departments of Physiology, Biochemistry, Pharmacology, Molecular Biology, Neurobiology, Bioengineering or Biostatistics. Interested persons should send a current curriculum vitae to

Keith W. Miller, D.Phil.
Department of Anaesthesia
Massachusetts General Hospital
Boston, MA 02114

These institutions are an affirmative action equal opportunity employer. Minorities and women are strongly urged to apply.

ANESTHESIA & ANALGESIA

Official Journal of the International Anesthesia Research Society

Editor-in-Chief
Ronald D. Miller
San Francisco, California

Associate Editor-in-Chief
John H. Tinker
Iowa City, Iowa

EDITORIAL BOARD

David R. Bevan
Vancouver, British Columbia, Canada

Thomas J. Gal
Charlottesville, Virginia

Kenjiro Mori
Kyoto, Japan

Walter S. Nimmo
Edinburgh, Scotland

Nathan L. Pace
Salt Lake City, Utah

Richard J. Palahniuk
Minneapolis, Minnesota

Michael F. Roizen
Chicago, Illinois

John J. Savarese
New York, New York

Hugo Van Aken
Leuven, Belgium

Section Editors

Ambulatory Anesthesia
Patricia A. Kapur
Los Angeles, California

Cardiovascular Anesthesia
Joseph G. Reves
Durham, North Carolina

Critical Care and Trauma
Ronald G. Pearl
Stanford, California

Neurosurgical Anesthesia
Donald S. Prough
Galveston, Texas

Obstetric Anesthesia
Mieczyslaw Finster
New York, New York

Pediatric Anesthesia
Paul R. Hickey
Boston, Massachusetts

Regional Anesthesia and Pain Management
Phillip O. Bridenbaugh
Cincinnati, Ohio

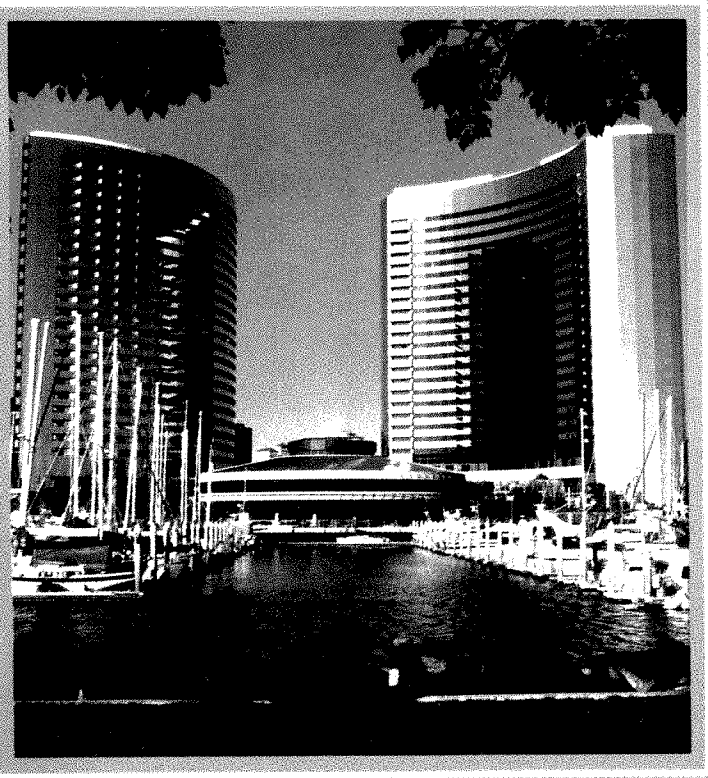
Book Reviews
Norig Ellison
Philadelphia, Pennsylvania

Managing Editor
King C. Kryger

Editorial Assistant
Christine A. Arturo

Manuscripts and editorial correspondence should be addressed to: King Kryger, PhD, Managing Editor, *Anesthesia & Analgesia*, 3497 Sacramento Street, San Francisco, CA 94118 [telephone: (415) 292-7964; FAX: (415) 292-5157]. For information concerning preparation of manuscripts, see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to Norig Ellison, MD, Book Review Editor, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.



IARS 67th CONGRESS

MARCH 19 -23, 1993

San Diego Marriott Hotel & Marina

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

CALL FOR PAPERS

If you have an abstract that you would like to have considered for inclusion on the scientific program (either oral or poster presentation), please complete and return the adjacent form. Abstract submission forms will be forwarded in May, 1992 to those requesting them. Scientific exhibit applications are also available. The deadline date for submission of abstracts is July 31, 1992. There is no absolute deadline for scientific exhibit submissions.

IARS
2 Summit Park Drive, #140
Cleveland, Ohio 44131
Fax #: (216) 642-1127
Phone #: (216) 642-1124

Re: 67th Congress, March 19-23,1993
San Diego Marriott Hotel & Marina
San Diego, California

Please send me
(_____) Abstract submission forms for paper/poster presentations
(_____) Scientific exhibit applications

Name_____

Address_____

_____

_____

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

Contents

Volume 75, Number 1, July 1992

EDITORIAL

1 **Anesthesia and Myocardial Ischemia: The Gains of the Past Have Largely Come From Control of Myocardial Oxygen Demand; The Breakthroughs of the Future Will Involve Optimizing Myocardial Oxygen Supply**
Michael Nugent

CARDIOVASCULAR ANESTHESIA

4 **Halothane Relaxes Previously Constricted Human Epicardial Coronary Artery Segments More Than Isoflurane**
Bruce A. Bollen, Robert E. McKlveen, and Joe A. Stevenson

9 **Halothane Relaxes Preconstricted Small and Medium Isolated Porcine Coronary Artery Segments More Than Isoflurane**
Bruce A. Bollen, Robert E. McKlveen, and Joe A. Stevenson

18 **Mechanisms of Renal Hemodynamic Impairment During Infrarenal Aortic Cross-Clamping**
Pascal Colson, Jean Ribstein, Jacques R. Séguin, Charles Marty-Ane, and Bernard Roquefeuil

NEUROSURGICAL ANESTHESIA

24 **Influence of Hydroxyethyl Starch on Coagulation in Patients During the Perioperative Period**
Yves Claes, Jan Van Hemelrijck, Mark Van Gerven, Jozef Arnout, Jos Vermylen, Burchard Weidler, and Hugo Van Aken

31 **Effects of Fentanyl on α-Aminoisobutyric Acid Transfer Across the Blood-Brain Barrier**
Oak Za Chi, Hwu Meei Wei, Mujahid Anwar, Arabinda K. Sinha, Sanford L. Klein, and Harvey R. Weiss

AMBULATORY ANESTHESIA

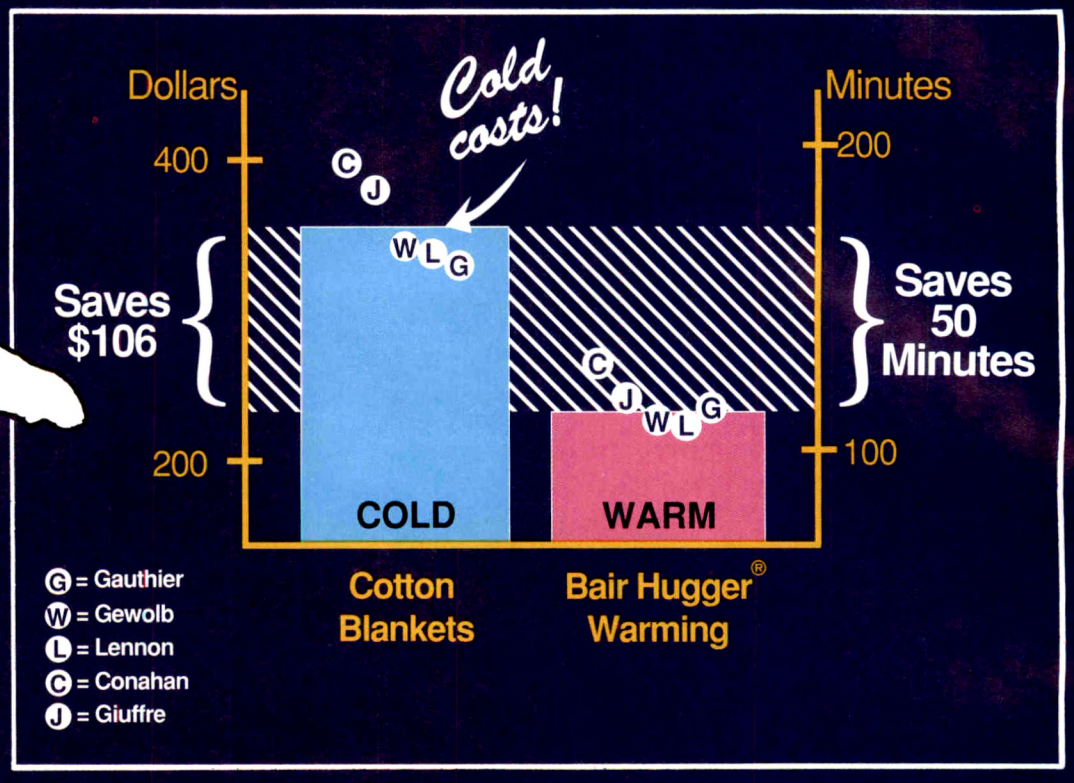
37 **Evaluation of the Endotracheal Intubating Conditions of Rocuronium (ORG 9426) and Succinylcholine in Outpatient Surgery**
Friedrich K. Pühringer, Karin S. Khuenl-Brady, Johann Koller, and Gottfried Mitterschiffthaler

41 **Intraoperative Patient-Controlled Analgesia: An Alternative to Physician Administration During Outpatient Monitored Anesthesia Care**
John Zelcer, Paul F. White, Steven Chester, John D. Paull, and Rowan Molnar

Anesthesia & Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. *© 1992 by the International Anesthesia Research Society.* *Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1992 applying to IARS members: USA and possessions, $95.00 per year; in all other countries, $120.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1992 applying to non-IARS members: Institutions, $150.00; nonmember individuals, $110.00. Outside the USA and possessions, please add $35.00 for surface postage and handling. For airmail, add $80.00 in USA, Canada, and Mexico; $70.00 for surface airlift to Europe; $85.00 for surface airlift to Japan; and $160.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia & Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.*

You can save $106 with every Bair Hug™!





For years, clinicians have relied on cotton blankets and other ineffective means to warm patients. Today, a compilation of data leads to a staggering conclusion. The additional PACU time required to rewarm patients by warm cotton blankets *costs your hospital $106 per patient.* In this era of DRG's and PPO's, this is an expense no hospital can afford.

The graph above illustrates data compiled from five independent studies: if patients are warm when admitted to the PACU or are *actively warmed* with Bair Hugger® Therapy, recovery time is shortened by an average of 50 minutes! This translates to $106 per patient.

Only Bair Hugger® Therapy actively warms patients; only Bair Hugger® Therapy expedites patient care in this way. Monitor your patient's temperature and treat patients with core temperatures of less than 36°C. What savings would *your* hospital enjoy, if you gave all your patients a Bair Hug? For a FREE TRIAL, call 1-800-733-7775 or your authorized dealer.

Bair Hugger

NORMOTHERMIA GUARANTEED

AUGUSTINE MEDICAL, INC.
PRACTICAL SOLUTIONS TO COMMON PROBLEMS IN ACUTE CARE™
10393 West 70th Street • Eden Prairie, Minnesota 55344
(612) 941-8866 (800) 733-7775

REFERENCES: Lennon RL, Hosking MP, Conover MA, Perkings WJ: Evaluation of a Forced-Air System for Warming Hypothermic Postoperative Patients. Anesthesia and Analgesia 70:424-427, 1990. Gauthier RL: Use of a Forced-Air Warming System for Intraoperative Warming. Anesthesiology 73:3A, 1990. Gewolb J, Hines R, Barash PG: A Survey of 3244 Admissions to the Post Anesthesia Recovery Room at a University Teaching Hospital. Anesthesiology 67:A471, 1987. Giuffre M, Finnie J, Lynam D, Smith D: Rewarming Postoperative Patients: Lights, Blankets or Forced Warm Air. Journal of Post Anesthesia Nursing Vol 6, No 6 387-393, Dec. 1991. Conahan TJ, et al: Airway Heating Reduces Recovery Time (Cost) in Outpatients. Anesthesiology 67:128-130, 1982. Vosskuhler R: PACU Costs in the United States. Augustine Medical Press, 1990.

© 1992 Augustine Medical. All rights reserved. AMIM-P-BHL-66-192

PEDIATRIC ANESTHESIA

45 **Efficacy of the FEF Colorimetric End-Tidal Carbon Dioxide Detector in Children**
Jeffrey S. Kelly, Randall D. Wilhoit, Raeford E. Brown, and Robert James

51 **Oral Midazolam in Children: Effect of Time and Adjunctive Therapy**
B. Craig Weldon, Mehernoor F. Watcha, and Paul F. White

OBSTETRIC ANESTHESIA

56 **Vasopressor Therapy for Hypotension During Epidural Anesthesia for Cesarean Section: Effects on Maternal and Fetal Flow Velocity Ratios**
Peter M. C. Wright, Mohammed Iftikhar, Kieran T. Fitzpatrick, James Moore, and William Thompson

64 **Combination of Low-Dose Epidural Morphine and Intramuscular Diclofenac Sodium in Postcesarean Analgesia**
Hsiao-Lun Sun, Chi-Chen Wu, Min-Shung Lin, Ching-Feng Chang, and Martin S. Mok

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

69 **Comparison Between Clonidine and Epinephrine Admixture to Lidocaine in Brachial Plexus Block**
Dorothee Gaumann, Alain Forster, Marthe Griessen, Walid Habre, Olivier Poinsot, and Dominique Della Santa

75 **Clinical Pharmacokinetics of R(+)- and S(−)-Mepivacaine After High Doses of Racemic Mepivacaine With Epinephrine in the Combined Psoas Compartment/Sciatic Nerve Block**
Tom B. Vree, Erik M. C. Beumer, Aart J. Lagerwerf, Marc A. M. Simon, and Mathieu J. M. Gielen

81 **Antinociceptive Effects of Phenobarbital in "Tail-Flick" Test and Deafferentation Pain**
José M. González-Darder, Antonio Ortega-Alvaro, Ignacio Ruz-Franzi, and Dolores Segura-Pastor

87 **Effects of Flumazenil on Intravenous Lidocaine-Induced Convulsions and Anticonvulsant Property of Diazepam in Rats**
Masataka Yokoyama, Kirk T. Benson, Kasumi Arakawa, and Hiroshi Goto

ORIGINAL ARTICLES

91 **Does Preoperative Anxiety Influence Gastric Fluid Volume and Acidity?**
Per E. Haavik, Eldar Søreide, Bjørn Hofstad, an Petter A. Steen

95 **Effects of Single-Dose Intravenous Omeprazole and Ranitidine on Gastric pH During General Anesthesia**
Peter G. Atanassoff, Eli Alon, and Thomas Pasc

99 **Ketorolac Does Not Decrease the MAC of Halothane or Depress Ventilation in Rats**
George F. Rich, Richard Schacterle, Jeffrey C. Moscicki, Cosmo A. DiFazio, and J. Milton Adams

103 **Effect of Chloride Transport Blockade on the MAC of Halothane in the Rat**
George F. Rich, Maryrose P. Sullivan, and J. Milton Adams

107 **Isoflurane Anesthesia Prevents Unconscious Learning**
R. Dwyer, H. L. Bennett, E. I. Eger II, and N. Peterson

113 **Oxygen Consumption and Carbon Dioxide Elimination After Release of Unilateral Lower Limb Pneumatic Tourniquets**
Tat-Leang Lee, William A. Tweed, and Bachan Singh

118 **Risk of Human Immunodeficiency Virus in Surgeons, Anesthesiologists, and Medical Students**
John M. Buergler, Robert Kim, Ronald A. Thisted, Stephan J. Cohn, J. Lance Lichtor, and Michael F. Roizen

CASE REPORTS

125 **Coagulopathy After Reinfusion of Autologous Scavenged Red Blood Cell**
David J. Murray, Kurt Gress, and Stuart L. Weinstein

PermaTail



THE PERMANENT MALPRACTICE PROTECTION PROGRAM
ONLY FOR SELECTED ANESTHESIOLOGISTS

PREFERRED
PHYSICIANS
MUTUAL
Risk Retention Group

204 Lucas Place
323 West 8th Street
Kansas City, Missouri 64105
Call Toll-free 800-562-5589

CASE REPORTS—*continued*

130 **Accidental Overdose of Systemic Morphine During Intended Refill of Intrathecal Infusion Device**
Christopher L. Wu and Richard B. Patt

133 **Unsuccessful Interpleural Analgesia in a Patient With Mesothelioma**
Zef A. Abraham

136 **Upper Airway Obstruction and Infant Botulism**
Andrew Oken, Steven Barnes, Peter Rock, and Lynne Maxwell

139 **Job's Syndrome: An Unusual Response to a Common Drug**
Louis M. Guzzi and John M. Stamatos

LETTERS TO THE EDITOR

141 **Is Epidural Anesthesia *Really* Better for Major Vascular Surgery?**
Benjamin H. Gorsky

141 ***In Response***
Kenneth J. Tuman, Robert J. McCarthy, and Anthony D. Ivankovich

142 **Mass Spectrometers and Infrared Gas Analyzers Interpret Bronchodilator Propellants as Anesthetic Gases**
Philip E. Bickler and Yung J. Sohn

143 **Masseter Muscle Spasm and the Diagnosis of Malignant Hyperthermia Susceptibility**
F. R. Ellis, P. M. Hopkins, P. J. Halsall, and A. S. Christian

144 ***In Response***
Abraham van der Spek

145 ***In Response***
Deepak Bose

146 **Isolated Masseter Muscle Spasm Versus Generalized Rigidity?**
Richard Kaplan, Matthew Becker, and Lynn Broadman

146 ***In Response***
Leena R. Patel, Deepak Bose, and Judith A. Littleford

147 **Ventilatory Effects of Clonidine**
R. Ooi and S. A. Feldman

147 **An Unusual Cause of Nasogastric Tube Obstruction**
Rafael Ortega

148 **Relief of Pain by Ketorolac or Alcohol?**
Duke B. Weeks

148 ***In Response***
David N. Vanos, Somayaji Ramamurthy, and Joan Hoffman

148 **Effects of Adenosine After Coronary Artery Bypass Surgery**
Atsuo F. Fukunaga and Tadaomi Miyamoto

149 ***In Response***
Sven-Erik Ricksten

150 **General Anesthesia and Toxemia of Pregnancy**
Andrew P. Harris

151 ***In Response***
Jaya Ramanathan, Phyllis Coleman, and Baha Sibai

152 **Venous Air Embolism During Spinal Instrumentation and Fusion in the Prone Position**
Terese T. Horlocker, Denise J. Wedel, and Roy F. Cucchiara

152 ***To the Editor***
Terry W. Latson

153 ***In Response***
Maurice S. Albin, Richard R. Ritter, and Leon Bunegin

153 **An Aid to Oral Intubation in Patients With Potential Cervical Spine Injuries**
Jerry P. Nolan and Michael E. Wilson

154 **Not All E Cylinders Were Created Equal**
J. Jeff Andrews and Robert V. Johnston, Jr.

154 **Anesthetic Drugs and the Emergency Department: One Teaching Institution's Response**
Jeffrey S. Kelly and Earl Schwartz

155 **Peer-Reviewed Anesthesiology Journals and Research**
Ian H. Lewis

156 ***In Response***
Nicholas M. Greene

156 **Another Approach With the Laryngeal Mask Airway**
David I. Thomas

The Osler Institute
Anesthesiology Board Review Courses
honoring Alon Winnie

July 4-9 and August 4-9, 1992 – Chicago

Aug. 1-3 – Los Angeles Aug. 14-16 – Atlanta †Sept. 14-19 – Boston

Now, special programs for written and oral boards

OBJECTIVES
- Improve basic and clinical knowledge of anesthesiology
- Assist residents and fellows to better organize for further study
- Prepare candidates to take their written and oral exams

METHODS
- HOME STUDY questions, answers, assignments and keywords
- SEMINAR with projection slides and lecture-note syllabus
- PRACTICE EXAMS for written and oral board exams

*The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities, but from people who are relatively unknown as well."**

Physiology
Respiratory Physiology
Cardiovascular Physiology
Neurophysiology
Hepatic & Renal Physiology
Acid-Base and Blood Gas

Pharmacology
Pharmacokinetics
Inhalation Anesthetics
Intravenous Anesthetics
Local Anesthetics
Muscle Relaxants
Central Nervous Drugs
Cardiac & Diuretic Drugs
Interactions & Genetics

Physical Sciences
Applied Anatomy
Physics and Gas Laws
Anesthesia Machines
Breathing Systems

Fundamentals
Preop. Evaluation & Prep.
Patient Monitoring
Airway Management
Fluid and Blood Therapy
Cardiopulmonary Disease
Hepatic & Renal Disease
Metabolic Disease
Recovery Room

Regional Anesthesia
Autonomic Blocks
Spinal and Epidural Blocks
Upper Extremity Blocks
Lower Extremity Blocks
Chronic Pain Management

Specialty Areas
Obstetric Anesthesia
Pediatric Anesthesia
Cardiac Anesthesia
Thoracic Anesthesia
Neuroanesthesia
Ophthalmic & E.N.T.
Geriatric and Outpatients

Solomon Aronson, M.D.
Ass't. Prof. of Anesthesiology
University of Chicago

Jonathan Benumof, M.D.
Professor of Anesthesiology
Univ. of California, San Diego

T. Andrew Bowdle, M.D.
Assoc. Professor of Anesthesiology
University of Washington

Eugene Cheng, M.D.
Ass't. Prof. of Anes. and Med.
Medical College of Wisconsin

Edward Czinn, M.D.
Clin. Ass't. Professor of Anes.
University of Illinois, Chicago

Hernando DeSoto, M.D.
Chief of Anesthesiology
Riverside Hospital, Jacksonville

Elizabeth Frost, M.D.
Professor of Anesthesiology
Albert Einstein College of Med.

Anthony Ivankovitch, M.D.
Prof. & Chmn. of Anesthesiology
Rush Medical College

Nells Jensen, M.D.
Associate in Anesthesiology
University of Iowa

Eugene Lipov, M.D.
Ass't. Prof. of Anesthesiology
Rush Medical College

David Lubarsky, M.D.
Ass't. Prof. of Anesthesiology
Duke University

Terence Murphy, M.D.
Professor of Anesthesiology
University of Washington

Michael Ritter, M.D.
Staff Anesthesiologist
St. John's Mercy Hosp., St. Louis

David Rothenberg, M.D.
Ass't. Prof. of Anesthesiology
Rush Medical College

Ramez Salem, M.D.
Clin. Prof. of Anesthesiology
University of Illinois, Chicago

Astride Seifen, M.D.
Professor of Anesthesiology
University of Arkansas

Daniel Siker, M.D.
Ass't. Prof. of Anes. and Ped.
Medical College of Wisconsin

Theodore Smith, M.D.
Professor of Anesthesiology
Loyola University

Alon Winnie, M.D.
Professor of Anesthesiology
University of Illinois, Chicago

Written Board Review
Lectures and written exam seminars
- Home-study keywords with discussions and questions with answers.
- Six-day lectures with syllabus.
- **Seminars for written exam questions.**
- July 4-9; September 14-19.

Oral Board Review
Mock oral exams and lectures
- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Six-day lectures with syllabus and concurrent mock oral exams most hours.
- **Registration includes one mock oral.**
- Extra public mock oral exam ($80), private mock oral exam ($110).
- July 4-9; August 4-9; September 14-19.

Oral Board Tutorial Days
Choose any days – groups limited to 24
- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Mock oral exams in groups **limited to 24.**
- **Includes one public mock oral per day.**
- Extra public mock oral exams ($80), private mock oral exams ($110).
- July 4-9; August 1-3; August 4-9; August 14-16; September 14-22.

Two-Part Board Review
Nine mock orals in any two courses
- Any course in 1992, plus any other within three years. One course may be up to six Oral Board Tutorial days of your choice.
- Choose between lectures and concurrent mock orals or written exam discussions.
- **Nine (9) mock oral exams in groups limited to 24 participants.**

Unconditional Guarantee
- If you fail the next Anesthesiology Board Exam you take after taking one of these courses, we will refund half of your last course registration fee and allow you to repeat the course once for FREE.
- This is NOT conditional upon you taking more than one course, or extra mock orals.
- Last year, after we first made this guarantee, **less than 2% requested a refund.**

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name _____

Address _____

City/State _____

Zip _____ Phone _____

☐ July 4-9, 1992 – Chicago
☐ August 1-3, 1992 – Los Angeles
☐ August 4-9, 1992 – Chicago
☐ August 14-16, 1992 – Atlanta
☐ September 14-19, 1992 – Boston
☐ Check enclosed for $ _____
☐ Please send **FREE SAMPLE**

Mail today to:
1094 East Dawn Drive, Dept. A207B
P.O. Box 2218
Terre Haute, IN 47802

Information
The Osler Institute
1094 East Dawn Drive, P.O. Box 2218
Terre Haute, IN, 47802
(800) 356-7537

†Plus mock orals only September 20-22.
** Comments by past Osler participants*

BOOK REVIEWS

157 **Lecture Notes on Anaesthetics by John N. Lunn**
Ronald J. Faust

157 **Moc Hoa by Larry P. Kammholz**
Alexander W. Gotta

157 **The Design of Analgesic Clinical Trials. Volume 18 in Advances in Pain Research and Therapy by Mitchell B. Max, Russell K. Portenoy, and Eugene M. Laska, eds.**
P. Prithvi Raj

158 **Blood Transfusion Therapy: A Physician's Handbook, 3rd ed., and Blood Transfusion Therapy: An Audiovisual Program, 2nd ed. by D. T. Pasciotto, ed.**
Kirk T. Benson

159 **Animal Pain by Charles E. Short and Alan Van Poznak, eds.**
Victor C. Lee

160 **Books Received**

A47 **A Guide for Authors**

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

The **International Anesthesia Research Society** is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: David R. Bevan, MA, MB, BChir, Michael K. Cahalan, MD, Douglas B. Craig, MD, FRCPC, Bruce F. Cullen, MD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Joseph G. Reves, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: E. Paul Didier, MD, Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, and B. B. Sankey, MD.

Anesthesia & Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1992 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices.

Subscription information for 1992 applying to IARS members: USA and possessions, $95.00 per year; in all other countries, $120.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. Associate Membership is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). Educational Membership (at a reduced price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2-, 3-, or 4-year period upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, OH 44131-2553.

Subscription information for 1992 applying to non-IARS members: Institutions, $150.00; nonmember individuals, $110.00. Outside the USA and possessions, please add $35.00 for surface postage and handling. For airmail, add $80.00 in USA, Canada, and Mexico; $70.00 for surface airlift to Europe; $85.00 for surface airlift to Japan; and $160.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia & Analgesia*, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Single issues: Single copy information is available from Elsevier Science Publishing Co., Inc., upon request. Back volume (all issues prior to 1983) information is available from the IARS.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See Classified Ads section for submission of classified ad material.

All articles published in this journal become the property of the International Anesthesia Research Society. This journal has been registered with the **Copyright Clearance Center, Inc.** Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the center the per copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. The appropriate fee should be forwarded with a copy of the first page of the article to the Copyright Clearance Center, Inc., 27 Congress Street, Salem, MA 01970. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

All inquiries regarding copyrighted material from this publication, other than reproduction through the Copyright Clearance Center, should be directed to: Rights and Permissions Department, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. FAX 212-633-3977.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) are processed through Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Prices are provided upon request.

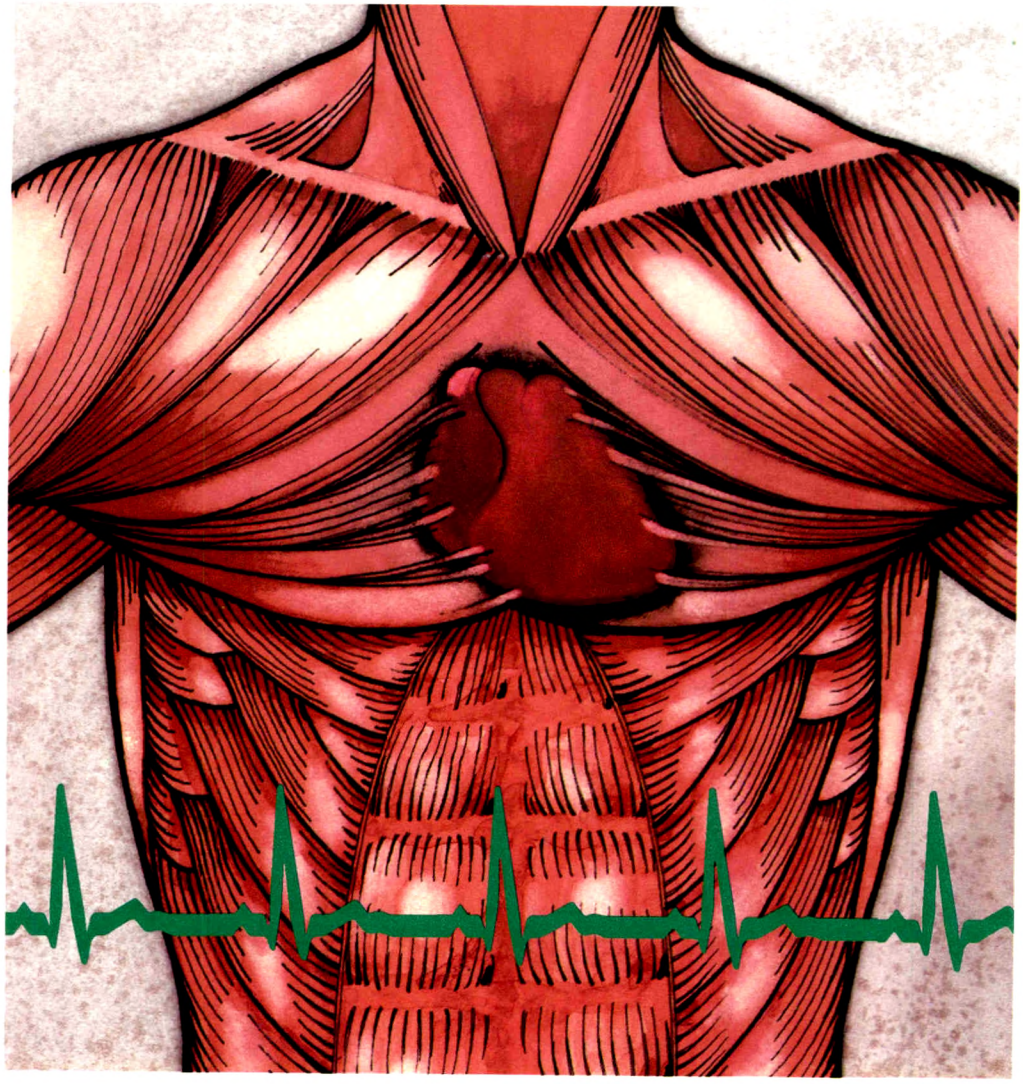
This journal is abstracted/indexed in: Biological Abstracts, Chemical Abstracts, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Index Medicus, ISI/Biomed, and Science Citation Index.

On line text is available through **BRS Colleague**, 8000 Westpark Drive, McLean, VA 22102. Telephone: (800) 289-4277.

This journal is printed on acid-free paper.

From Burroughs Wellcome Co.
A Long-Acting Neuromuscular Blocker

Excellent CV Stability



NUROMAX® INJECTION
(doxacurium chloride) 1 mg/mL

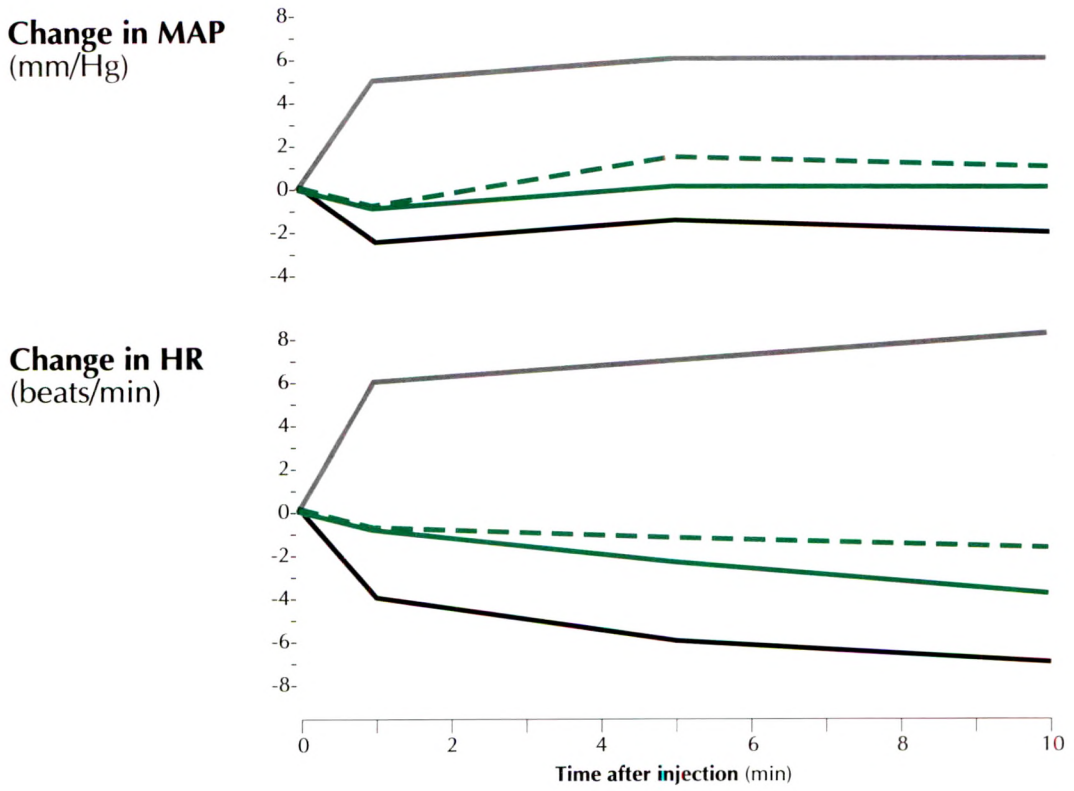
Please see brief summary of full prescribing information.

A Long-Acting Neuromuscular Blocker

NUROMAX® INJECTION
(doxacurium chloride)

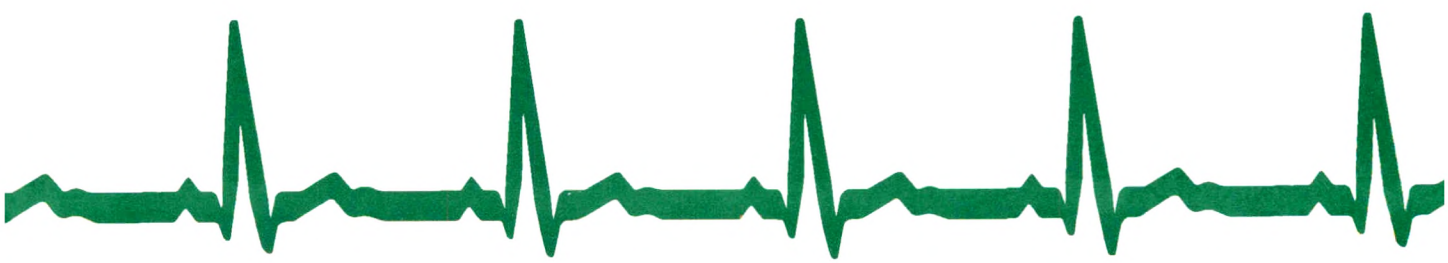
Excellent CV Stability

Cardiovascular stability comparable with vecuronium



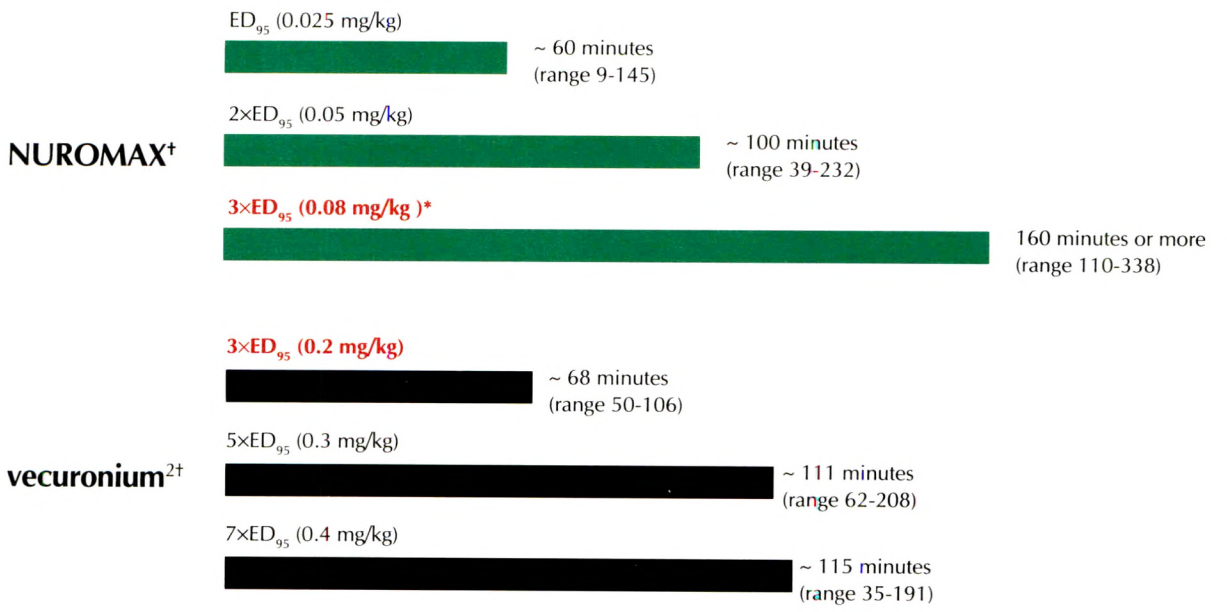
Emmott et al[1] compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075 mg/kg in 36 CABG patients (9 patients, each group).
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration.
All routine cardiac and vasoactive medications were continued up to the morning of surgery.

- doxacurium 0.037 mg/kg
- doxacurium 0.075 mg/kg
- pancuronium 0.09 mg/kg
- vecuronium 0.075 mg/kg



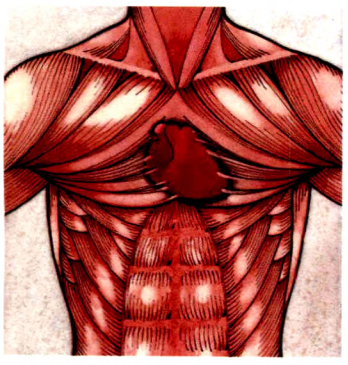
Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)



*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.
†Numbers shown are not directly comparable since these data have been compiled from different study populations.

- **Cardiovascular stability comparable with normal saline** [3]
- **Noncumulative**
- **Ready-to-use solution**
- **Vials stored at room temperature, no refrigeration required**
- **Supplied as a 5 mL vial, 1 mg/mL**



NUROMAX® INJECTION

(doxacurium chloride) 1 mg/mL

Excellent for Long CV Procedures



Please see brief summary of full prescribing information.

NUROMAX® INJECTION
(DOXACURIUM CHLORIDE)

Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing ≥ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulas:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation. Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy. Nuromax has not been studied in patients with asthma. No data are available to support the use of Nuromax by intramuscular injection. **Renal and Hepatic Disease:** Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients. **Obesity:** Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing ≥ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). **Malignant Hyperthermia (MH):** In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. **Long-Term Use in the Intensive Care Unit (ICU):** No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU. **Drug Interactions:** Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax. The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied. There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents. Isoflurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m²) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m²) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m²) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section. **Nursing Mothers:** It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman. **Pediatric Use:** Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age. **Geriatric Use:** Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications. **Observed in Clinical Trials:** Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular*:	hypotension,† flushing,† ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

* Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

† 0.3% incidence. All other reactions unmarked were ≤ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (*i.e.*, at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

Adults: *Initial Dose:* When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Copr. © 1991 Burroughs Wellcome Co. All rights reserved. NM-Y03102

EDITORIAL

Anesthesia and Myocardial Ischemia: The Gains of the Past Have Largely Come From Control of Myocardial Oxygen Demand; The Breakthroughs of the Future Will Involve Optimizing Myocardial Oxygen Supply

Michael Nugent, MD
Medical College of Ohio, Toledo, Ohio

The introduction of anesthetic techniques that use high-dose narcotics or β-adrenergic blockers, or both, to attenuate adrenergic responses to intraoperative stimulation has facilitated management of the patient at risk for intraoperative myocardial ischemia and infarction. Slogoff and Keats (1) have shown a difference in the occurrence of myocardial ischemia and perioperative myocardial infarction, depending on the adequacy of hemodynamic control by the anesthesiologist during coronary artery bypass grafting surgery (2). Perioperative Holter monitoring for myocardial ischemia has demonstrated that ischemic episodes occur twice as often preoperatively and postoperatively than they do intraoperatively. Modern anesthetic interventions may help control ischemic episodes during the intraoperative period (3). A most important finding is that the majority of intraoperative ischemic episodes occur in the absence of hemodynamic aberrations, such as tachycardia, hypertension, or hypotension. This implies that many of the episodes of intraoperative myocardial ischemia occur because of a decrease in myocardial oxygen supply rather than an increase in myocardial oxygen demand.

In patients with coronary artery disease, obstructions occur in the large epicardial coronary vessels, the same vessels that are bypassed during coronary artery bypass surgery. Some stenotic lesions are concentric, but most are eccentric in location, with a rim of vessel unaffected by the atheromata. Tone in this rim of tissue not involved with plaque can be altered by naturally occurring dilators and constrictors, resulting in a dynamic stenosis that can change in diameter. When atherosclerotic plaques rupture, platelets then aggregate and form adherent thrombi. Ruptured plaques and thrombus formation are regarded as the usual etiology of unstable angina (4,5). Constriction of coronary vessels can occur with mediators of spasm, such as thromboxane and serotonin. The endothelium of large epicardial vessels secretes several vasodilators, such as prostacyclin, endothelium-derived relaxing factor, and hyperpolarizing factor, as well as vasoconstrictors, such as endothelin and endothelium-derived constricting factor. In the past few weeks, the effect of volatile anesthetics on endothelium-dependent vasodilation has been studied. Blaise et al. (6) found that attenuation by isoflurane of the contractile response of isolated canine coronary rings to d-5-hydroxytryptamine and prostaglandin $F_{2\alpha}$ was dependent on the presence of endothelium. This attenuation was only slightly reduced by pretreatment of the vascular rings with indomethacin, and they therefore postulated that the effect of isoflurane occurred through the release of endothelium-derived relaxing factor. Isoflurane and halothane attenuate coronary artery constriction evoked by serotonin in isolated vessels and in intact pigs (7). Furthermore, halothane reduces the response of preconstricted rabbit and canine vascular rings to acetylcholine and bradykinin. Muldoon et al. (8) have suggested that halothane inhibits the release or action of endothelium-derived relaxing factor, but they also demonstrated a direct action of halothane on vascular smooth muscle when endothelium had been removed from the vessels.

It is important to note that neither halothane nor isoflurane has any effect on the basal tension of isolated canine femoral arteries or rabbit or rat aortic rings. These anesthetics can only modify the tension of contracted rings. This is in contrast to nitroglycerin, which can cause dilation of a coronary vessel by direct effect on vascular smooth muscle via nitric oxide donation. In this issue of *Anesthesia & Analgesia*,

Accepted for publication February 27, 1992.
Address correspondence to Dr. Nugent, Department of Anesthesiology, Medical College of Ohio, 3000 Arlington Avenue, PO Box 10008, Toledo, OH 43699-0008.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Bollen et al. (9) found that halothane relaxes preconstricted small and medium isolated porcine coronary artery segments more than isoflurane. They have expanded on their earlier study, which examined the effects of these drugs on large epicardial coronary porcine arteries (10). It is important to do this technically difficult work in smaller vessels because some drugs have a differing effect in small and medium coronary arteries compared with large epicardial coronary arteries. Bollen et al. (9) have studied the effects of potent inhaled anesthetics on epicardial vessels large enough to not be an important factor in determining coronary vascular resistance; however, their findings have nothing to do with the mechanism of intercoronary steal, which involves the relaxation of small intramyocardial resistance vessels rather than the small and medium epicardial vessels that they studied. Also in this issue of *Anesthesia & Analgesia,* Bollen et al. (11) found that halothane relaxes previously constricted epicardial human coronary artery segments more than isoflurane. In essence, the authors repeated their 1987 porcine study (10) but in human coronary arteries from recipient patients whose hearts were removed before transplantation. This study validates the porcine model for studying coronary artery vascular tone as it relates to humans. They studied the effects of isoflurane and halothane on preconstricted coronary arteries from patients with ischemic cardiomyopathy, two with viral cardiomyopathy and two with atrioventricular canal malformations with pulmonary hypertension. One should find a variable degree of endothelial integrity in this group of patients, yet responses to the inhaled anesthetics were consistent. Villeneuve et al. (12) have reported similar findings in the human heart, but they studied only one concentration of halothane and isoflurane, whereas Bollen et al. studied two concentrations.

These studies use an established model with scientific validity, and their findings are consistent with other studies that examined the effects of these potent inhaled anesthetics with regard to their possible ability to reverse coronary spasm. In contrast to nitroglycerin, isoflurane and halothane do not alter resting coronary artery tone, and their effects may be seen only in preconstricted large epicardial coronary vessels.

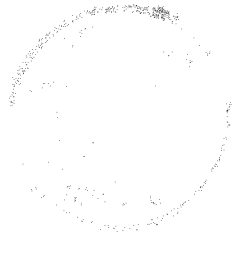
In their paper "Halothane Relaxes Preconstricted Small and Medium Isolated Porcine Coronary Artery Segments More Than Isoflurane" (9), Bollen et al. compare the capacity of halothane versus isoflurane to inhibit the activation of calcium channels by BAY K8644. These findings support the fairly well-established fact that halothane does depress calcium influx through slow calcium channels. It is important to note that halothane-induced relaxation of potassium constriction by BAY K8644 was not complete; therefore, halothane may well act through additional mechanisms to relax previously constricted coronary arteries. Because there is no voltage-activated calcium channel in endothelial cells, future studies need to evaluate the possible effects of halothane on the endothelial calcium-dependent potassium channels or its possible effects on G proteins, which are a complex of proteins that mediate intracellular responses to some agonists and modulate adenylate cyclase activity (13).

Calcium entry blockers are definitely effective therapeutic regimens for awake patients who have angina pectoris. By giving a patient calcium entry blockers during a treadmill stress test, the ischemic threshold is reduced. In the intraoperative setting, calcium entry blockers are not effective in decreasing the incidence of intraoperative ischemic episodes (14). Some protection from mediators of spasm may possibly occur because of the presence of potent inhaled anesthetics or simply because in the anesthetic setting, catecholamine levels are decreased compared with the exercising patient. Future studies will not only examine the effects of anesthetics and drugs on large epicardial coronary artery tone but will also study their effects on intracoronary thrombus formation. Halothane, not isoflurane or enflurane, decreases the frequency of intracoronary thrombus formation in stenosed dog coronary arteries (15). The pioneering studies by Bollen et al. (9,11), examining anesthetic effects on large epicardial coronary arteries, may lead the way to the development of new methodologies for blocking unwanted changes in large epicardial coronary artery tone in the perioperative period.

References

1. Slogoff S, Keats A. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
2. Lowenstein E. Perianesthetic ischemic episodes cause myocardial infarction in humans—a hypothesis confirmed (editorial). Anesthesiology 1985;62:103–6.
3. Knight AA, Hollenberg M, London MJ, et al. Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 1988;68:681–8.
4. Gotoh K, Minamino T, Katoh O, et al. The role of intracoronary thrombus in unstable angina: angiographic assessment and thrombolytic therapy during ongoing anginal attacks. Circulation 1988;77:526–34.
5. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Circulation 1985;71:699–708.
6. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
7. Witzeling TM, Sill JC, Hughes JM, Blaise GA, Nugent M, Rorie DK. Isoflurane and halothane attenuate coronary artery con-

striction evoked by serotonin in isolated porcine vessels and in intact pigs. Anesthesiology 1990;73:100–8.
8. Muldoon SM, Hart JL, Bowen KA, Freas W. Attenuation of endothelium-mediated vasodilation by halothane. Anesthesiology 1988;68:31–7.
9. Bollen BA, McKlveen RE, Stevenson JA. Halothane relaxes preconstricted small and medium isolated porcine coronary artery segments more than isoflurane. Anesth Analg 1992;75: 9–17.
10. Bollen BA, Tinker JH, Hermsmeyer K. Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 1987;66:748–52.
11. Bollen BA, McKlveen RE, Stevenson JA. Halothane relaxes previously constricted human epicardial coronary artery segments more than isoflurane. Anesth Analg 1992;75:4–8.
12. Villeneuve E, Blaise G, Sill JC, Guerard MJ, Buluran J, Girard D. Halothane 1.5 MAC, isoflurane 1.5 MAC and the contractile response of coronary arteries obtained from human hearts. Anesth Analg 1991;72:454–61.
13. Morgan NG. Cell signaling. New York: The Guilford Press, 1990:35–57.
14. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia. Anesthesiology 1988;68:676–80.
15. Bertha BG, Folts JD, Nugent M, et al. Halothane, but not isoflurane or enflurane, protects against spontaneous and epinephrine-exacerbated acute thrombus formation in stenosed dog coronary arteries. Anesthesiology 1989;71:96–102.



Halothane Relaxes Previously Constricted Human Epicardial Coronary Artery Segments More Than Isoflurane

Bruce A. Bollen, MD, Robert E. McKlveen, MD, and Joe A. Stevenson, AA

Department of Anesthesia, University of Iowa, Iowa City, Iowa and Cardiovascular Anesthesia Group, Department of Anesthesia, Stanford University, Stanford, California

To compare the vasodilatory effects of isoflurane versus halothane on coronary arteries in vitro, we studied the capacity of isoflurane and halothane to relax resting and previously constricted human coronary artery segments with use of in vitro tension recording. Human epicardial coronary artery segments (1.5–2.0 mm outside diameter) were obtained from hearts excised from recipient patients at time of heart transplantation. The effects of 0.5%, 1.0%, 2.0%, and 3.0% isoflurane or halothane on resting coronary artery segments stretched to their optimal resting tension were determined. Next, after removal of anesthetic from the bathing solution, the segments were constricted with K^+ (60 mM), and this contraction was allowed to plateau. The arteries were then again exposed to isoflurane or halothane at 0.5%, 1.0%, 2.0%, and 3.0% concentrations. Isoflurane and halothane had no effect on noncontracted coronary artery segments stretched to their optimal resting tension. Halothane caused significant relaxation of K^+-induced (60 mM) contractions at 2.0% and 3.0% but not at lower concentrations. Isoflurane did not cause significant relaxation of K^+-induced (60 mM) contractions at any concentration studied. Our studies indicate that under the conditions studied, isoflurane at clinically relevant concentrations is not a significant coronary dilator.

(Anesth Analg 1992;75:4–8)

In vitro studies of the effects of halothane and isoflurane on coronary artery segments have generally been limited to porcine and canine coronary models (1–4). Unfortunately, these models have yielded conflicting results. Blaise and colleagues (2,3) reported that isoflurane induced endothelium-dependent attenuation of serotonin-evoked contraction in the canine but not the porcine coronary artery model. Bollen et al. (1) showed halothane to be more potent than isoflurane in relaxing previously constricted porcine epicardial coronary arteries. There have been few such in vitro studies on human coronary arteries (5). We compared the in vitro effects of clinically relevant isoflurane and halothane concentrations on resting and previously constricted human epicardial coronary artery segments (1.5–2.0 mm outside diameter [OD]) in a dose-response design. Our goal was to determine whether these anesthetics had a significant direct vasodilatory effect on human epicardial coronary arteries and, if so, to determine their relative potency.

Accepted for publication February 20, 1992.

This work was supported in part by the B. B. Sankey Research Award and Veterans Administration Research Advisory Group.

Address correspondence to Dr. Bollen, Department of Anesthesia, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Methods

Human hearts obtained from recipient patients at the time of heart transplantation at Stanford University were placed in cool (4°C) ionic solution for mammals (ISM) (mM composition: 130 NaCl, 16 $NaHCO_3$, 0.5 NaH_2PO_4, 4.7 KCl, 1.8 $CaCl_2$, 0.4 $MgCl_2$, 0.4 $MgSO_4$, 13 HEPES, and 5.5 dextrose; pH 7.4). The study was approved by the Stanford University Human Subject Committee. Coronary epicardial arteries from the circumflex and left anterior descending coronary arteries were dissected free with use of a dissecting microscope. One-millimeter-wide circular ring arterial segments 1.5–2.0 mm OD were cut, threaded with stainless steel hooks, and suspended in temperature-controlled, constant-flow muscle chambers. High-fidelity force transducers (Akers, Norway; sensitivity 1–9000 mg) were used for tension recording. Muscle chambers were perfused with oxygenated (95% O_2–5% CO_2) ISM at 37°C (1). The optimal resting tension was determined with use of repeated K^+-induced (60 mM) contractions, followed by a 30-min washout with ISM. We used K^+ (60 mM) because we found K^+ (60 mM) in human epicardial coronary arteries to cause contractile tensions similar to those seen previously by Bollen et al.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Anesthetic Effect on Optimally Stretched Resting Human Coronary Artery Segments

	Change in resting tension as percent maximal K^+-induced (60 mM) contraction at anesthetic concentrations of 0%, 0.5%, 1.0%, 2.0%, and 3.0%				
	0	0.5	1.0	2.0	3.0
Halothane (n = 4, 11 arterial segments)	0	−0.3 ± 1.7	−1.6 ± 1.3	−1.9 ± 1.0	0.9 ± 3.2
Isoflurane (n = 4, 12 arterial segments)	0	−1.5 ± 0.4	−1.8 ± 0.8	−0.8 ± 0.6	−1.0 ± 0.6

Data are presented as mean values ± SEM. No results were significantly different (actual $P < 0.0125$) compared with 0%; overall $P < 0.05$ maintained by Bonferroni multiple-comparison procedure.

(1) in pig coronary arteries with use of K^+ (30 mM) (6).

To determine the effects of halothane and isoflurane on noncontracted (resting) coronary artery segments stretched to their optimal resting tension, resting coronary artery segments at optimal resting tension were exposed to ISM saturated with 0.5%, 1.0%, 2.0%, and 3.0% vol/vol halothane or isoflurane, and the effect on tension was measured. Anesthetic was then removed from the system, and the vessels were allowed to reequilibrate for a minimum of 30 min.

After anesthetic washout, the coronary segments were constricted with K^+ (60 mM) and contraction was allowed to plateau. After stabilization of contraction, halothane or isoflurane was added in incremental steps to achieve concentrations calculated for K^+ (60 mM) saturated with 0.5%, 1.0%, 2.0%, and 3.0% vol/vol, and the effect on tension was measured. After exposure to 3% anesthetic for 20 min, or until stabilization of effect, anesthetic was discontinued, and the K^+-induced (60 mM) contraction was allowed to restabilize. Arterial segments from the last three hearts studied were then exposed to 3% of the alternate anesthetic and the effect on tension was measured.

Isoflurane and halothane were added in incremental steps to achieve steady-state concentrations. Randomization of the order in which anesthetic concentrations were given was not done because of concern that prolonged effects from higher concentrations might influence results seen with lower concentrations (7). Isoflurane and halothane were added as previously described (1). The apparatus was sealed to maintain the appropriate anesthetic concentration. For every experiment at each anesthetic concentration, electron-capture gas chromatographic measurement using heptane extraction was performed to document actual anesthetic concentrations in the ISM bathing each arterial segment (1,8). Expected concentrations to be studied in micrograms of anesthetic per milliliter of ISM were as follows: halothane 32, 64, 128, and 192 and isoflurane 21, 43, 86, and 128. Based on anesthetic solubility coefficients, these concentrations correspond to calculated concentrations of anesthetic in ISM at 37°C saturated with 0.5%, 1.0%, 2.0%, and 3.0% of the volatile agent, respectively (9).

Four to eight coronary segments were studied in separate identical muscle chambers at any one time. Return of K^+-induced contraction to preanesthetic level after anesthetic exposure served as the internal control for each segment. Previous work (1) has documented stability of this preparation over time. Thirty-four coronary artery segments from six human hearts (n = 6) were studied. The effect of anesthetics on resting coronary tension was not determined for

Table 2. Anesthetic Effect on K^+ Contractile Tension in Human Coronary Artery Segments

	Percent maximal tension at anesthetic concentrations of 0%, 0.5%, 1.0%, 2.0%, and 3.0%				
	0	0.5	1.0	2.0	3.0
Halothane (n = 6, 16 arterial segments)	100	91.8 ± 4.6	82.2 ± 6.6	55.6 ± 8.9[a]	28.9 ± 7.4[a,b]
Halothane-isoflurane (3% posthalothane) (n = 3, 7 arterial segments)					72.2 ± 12.7
Isoflurane (n = 6, 18 arterial segments)	100	98.2 ± 4.4	96.0 ± 6.7	91.3 ± 8.9	80.2 ± 7.4
Isoflurane-halothane (3% postisoflurane) (n = 3, 9 arterial segments)					59.9 ± 3.9

Data are presented as mean values ± SEM.
[a]Significantly different (actual $P < 0.0125$) compared with 0%; overall $P < 0.05$ maintained by Bonferroni multiple-comparison procedure.
[b]Significantly different (actual $P < 0.0125$) compared with isoflurane at same concentration; overall $P < 0.05$ maintained by Bonferroni multiple-comparison procedure.

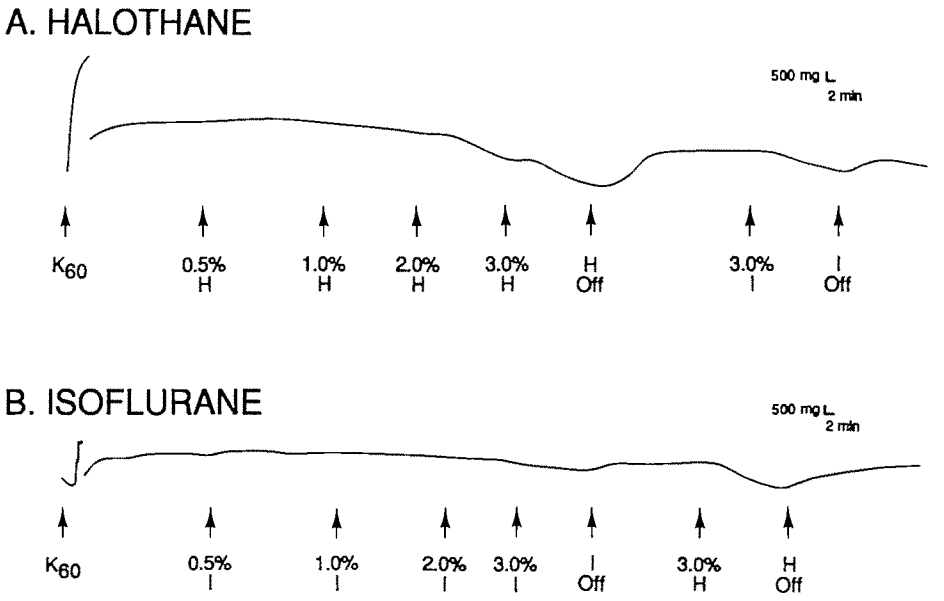


Figure 1. A. KCl-induced (60 mM) (K_{60}) sustained contraction of a human coronary artery segment, followed by exposure to halothane (H) in a dose-dependent manner. Isoflurane (I) 3.0% was added after removal of halothane (H Off) and contraction restabilized. **B.** KCl-induced (60 mM) contraction, followed by exposure to isoflurane (I). Halothane (H) 3.0% was added after removal of isoflurane (I Off), and contraction restabilized. Halothane 3.0% after removal of isoflurane induced greater relaxation than did 3.0% isoflurane.

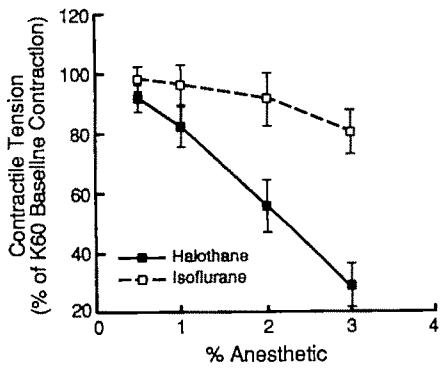


Figure 2. Anesthetic effect on K^+-constricted (60 mM) (K_{60}) human coronary artery segments. Note concentration-dependent response to halothane and isoflurane. Measured tension is expressed as percent maximal K^+-induced (60 mM) contraction.

vessels from the first two hearts studied. Etiologies of end-stage heart disease in hearts studied were ischemic cardiomyopathy (n = 2), viral cardiomyopathy (n = 2), and atrioventricular canal malformations with pulmonary hypertension (n = 2).

Data are presented as percent maximal tension for K^+-induced (60 mM) contractions; for each experiment, n refers to the number of human hearts studied. For statistical analysis, results from multiple coronary artery segments from the same heart studied under identical conditions were first averaged to obtain a mean value for each heart. Results are expressed as mean values ± SEM. Repeated measures analysis of variance was used to analyze data. Single-tail t-tests when appropriate were used to obtain P values. Where appropriate, the Bonferroni multiple-comparison procedures were used to maintain an overall significance level of $P < 0.05$.

Results

Results are presented in Tables 1 and 2 and Figures 1 and 2. Neither halothane nor isoflurane had a significant effect on noncontracted human coronary artery segments stretched to their optimal resting tension. Halothane caused significant relaxation of K^+-induced (60 mM) contractions at 2.0% and 3.0% ($P < 0.0125$). Isoflurane did not cause significant relaxation of K^+-induced (60 mM) contractions at any concentration studied ($P < 0.0125$). Halothane caused significantly more relaxation than isoflurane of K^+-induced (60 mM) contractions at 3.0% ($P < 0.0125$).

Potassium-constricted (60 mM) coronary artery segments exposed to 0.5%, 1.0%, 2.0%, and 3.0% halothane, followed later by exposure to 3.0% isoflurane after halothane washout, showed significantly more relaxation with 3.0% halothane than with 3.0% isoflurane ($P < 0.05$). Potassium-constricted (60 mM) coronary artery segments exposed to 0.5%, 1.0%, 2.0%, and 3.0% isoflurane, followed later by 3.0% halothane after isoflurane washout, also exhibited significantly more relaxation with 3.0% halothane than with 3.0% isoflurane ($P < 0.05$).

Optimal resting tensions (±SEM) determined for the vessels studied were 1485 ± 39 mg. Average tension (±SEM) for K^+-induced (60 mM) contractions

was 5132 ± 188 mg. Concentrations refer to goal concentrations for isoflurane or halothane at 0.5%, 1.0%, 2.0%, and 3.0% vol/vol saturating the solution bathing the coronary artery segments. Actual measured anesthetic concentrations (±SEM) in solution for halothane were 0.55% ± 0.01%, 1.09% ± 0.03%, 2.20% ± 0.06%, and 3.6% ± 0.15%. Concentrations for isoflurane were 0.55% ± 0.01%, 1.01% ± 0.02%, 1.96% ± 0.05%, and 3.07% ± 0.09%.

Discussion

We have shown that halothane is more potent than isoflurane in relaxing human epicardial coronary artery segments of 1.5–2.0 mm OD that were previously constricted with K^+ (60 mM). Halothane caused significant relaxation at lower concentrations than isoflurane. Neither halothane nor isoflurane had an effect on resting, nonconstricted coronary arteries. Our results expand recent work by Villeneuve et al. (5) that showed that 1.5 MAC halothane but not 1.5 MAC isoflurane attenuated contractile responses of human coronary artery ring segments to mediators of coronary vasoconstriction. Our work shows that halothane and isoflurane effects on human coronary segments are dose dependent and that halothane causes greater relaxation of these epicardial coronary arteries.

These results are similar to those we previously observed (1) studying porcine coronary arteries (1.5–2.0 mm OD). In that study the percent maximal tension of arteries preconstricted with K^+ (30 mM) and exposed to halothane at 0%, 0.5%, 1.0%, 2.0%, and 3.0% was 100%, 100%, 89%, 52%, and 24%, respectively, with relaxation achieving statistical significance at 1.5%, 2.0%, and 3.0% halothane. This compares favorably with the current results in humans in which the percent maximal tension of arteries preconstricted with K^+ (60 mM) and exposed to halothane at 0%, 0.5%, 1.0%, 2.0%, and 3.0% was 100%, 91.8%, 82.2%, 55.6%, and 28.9%, respectively, achieving significance at 2.0% and 3.0%. For isoflurane, the percent maximal tension of porcine coronary arteries (1.5–2.0 mm OD) preconstricted with K^+ and exposed to 0%, 0.5%, 1.0%, 2.0%, and 3.0% isoflurane was 100%, 108%, 108%, 98%, and 83% versus 100%, 98.2%, 96.0%, 91.3%, and 80.2% for human coronary arteries. Although isoflurane-induced relaxation did achieve significance at 3.0% in our previous porcine experiments, isoflurane did not achieve significant relaxation at any concentration tested in the present experiments on human coronary arteries. The results from porcine versus human experiments are very similar. Lack of significant relaxation by 3% isoflurane in human coronary segments may reflect the relatively small number of the human versus porcine experiments. The difference in concentration of K^+ used in the human versus porcine experiments was an attempt to achieve similar contractile tensions (5132 ± 188 mg in the human model versus 4680 ± 236 mg in the porcine model). Having to choose between equalizing K^+ concentrations or the magnitude of contraction between our previous porcine and the current human experiments, we decided that it was most appropriate to control the magnitude of contraction. This removed potential error caused by the possibility that the magnitude of contraction might affect the observed anesthetic effect.

Isoflurane and halothane have a similar effect on porcine versus human epicardial coronary artery segments that have been preconstricted with K^+. These results may not apply to smaller coronary arteries; that is, large and small coronary arteries may show a different response to the same drug (10,11). Also, our human coronary segments came from severely diseased hearts, whereas our porcine segments came from normal animals.

In vitro techniques are helpful in defining the physiologic effects of drugs on specific models. We observed no effect of halothane or isoflurane on resting, nonconstricted coronary segments. These segments were removed from their normal in vivo environment where arterial tone is dynamic and influenced by many factors. Coronary vessels in vivo may respond differently to anesthetics, depending on the particular level of vascular tone at the time of the experiment. Sill et al. (12) examined in vivo epicardial coronary arteries in dogs and reported no effect of isoflurane on resting large epicardial coronary arteries. Our in vitro results are in agreement. From our studies and those of Sill et al., it appears that isoflurane and halothane have no significant effect on resting epicardial coronary arteries. In the presence of increased coronary tone, isoflurane in vitro is not a potent coronary artery dilator. In contrast, halothane did cause relaxation of constricted coronary arteries at high concentrations.

We have chosen to compare halothane and isoflurane at equal concentrations (% vol/vol) and not at MAC increments. MAC (as % anesthetic) is a measure of potency of an agent as an anesthetic based on movement responses to noxious stimuli and not based on cardiovascular responses. MAC itself is derived by studying dose-response ranges of anesthetic concentrations as % vol/vol. We believe that the same should be done when comparing the anesthetic effects on other physiologic parameters, which is why we performed dose-response studies. Our % vol/vol method allows direct comparisons in a clinically relevant fashion because vaporizers are calibrated by percent agent delivered not by MAC fraction deliv-

ered. It is, of course, possible to analyze our results using MAC fractions. When we did this, halothane still caused significantly more relaxation than isoflurane in the previously constricted human epicardial coronary arteries.

In conclusion, we studied the dose-response effects of halothane and isoflurane on human epicardial coronary artery segments (1.5–2.0 mm OD) at rest and constricted with K^+ (60 mM). We conclude that neither halothane nor isoflurane affects resting tension. Halothane caused more relaxation than did isoflurane of K^+-constricted human epicardial coronary arteries. We conclude that isoflurane is not a potent dilator of human epicardial coronary arteries in vitro.

References

1. Bollen BA, Tinker JH, Hermsmeyer K. Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 1987;66:748–52.
2. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
3. Witzeling TM, Sill JC, Hughes JM, Blaise GA, Nugent M, Rorie DK. Isoflurane and halothane attenuate coronary artery constriction evoked by serotonin in isolated porcine vessels and in intact pigs. Anesthesiology 1990;73:100–8.
4. Blaise GA, Witzeling TM, Sill JC, Vinay P, Vanhoutte PM. Fentanyl is devoid of major effects on coronary vasoreactivity and myocardial metabolism in experimental animals. Anesthesiology 1990;73:535–41.
5. Villeneuve E, Blaise G, Sill JC, Guerard MJ, Buluran J, Girard D. Halothane 1.5 MAC, isoflurane 1.5 MAC and the contractile response of coronary arteries obtained from human hearts. Anesth Analg 1991;72:454–61.
6. Ginsburg R, Bristow MR, Davis K, Dibias A, Billingham ME. Quantitative pharmacologic responses of normal and atherosclerotic isolated human epicardial coronary arteries. Circulation 1984;69:430–40.
7. Spiss C, Smith C, Tsujimoto G, Hoffman B, Maze M. Prolonged hyporesponsiveness of vascular smooth muscle contraction after halothane anesthesia in rabbits. Anesth Analg 1985;64:1–6.
8. Davis D. A method of gas chromatography using electroncapture detection for the determination of blood concentration of halothane, chloroform and trichloroethylene. Br J Anaesth 1978;50:147–55.
9. Lerman J, Willis M, Gregory G, Eger E. Osmolarity determines the solubility of anesthetics in aqueous solutions at 37°C. Anesthesiology 1983;59:554–8.
10. Marcus ML, Chilian MC, Hiroshi K, Dellsperger KC, Eastham CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. Circulation 1990;82: 1–7.
11. Schnaar RL, Sparks HV. Response of large and small coronary arteries to nitroglycerin, $NaNO_2$, and adenosine. Am J Physiol 1972;223:223–8.
12. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. Anesthesiology 1987;66:273–9.

Halothane Relaxes Preconstricted Small and Medium Isolated Porcine Coronary Artery Segments More Than Isoflurane

Bruce A. Bollen, MD, Robert E. McKlveen, MD, and Joe A. Stevenson, AA

Department of Anesthesia, University of Iowa, Iowa City, Iowa and Cardiovascular Anesthesia Group, Department of Anesthesia, Stanford University, Stanford, California

To compare the putative vasodilatory effects of isoflurane versus halothane on porcine coronary arteries, we studied the capacity of isoflurane and halothane to relax K^+-constricted (30 mM) small (0.5–1.0 mm outside diameter [OD]) and medium (1.0–1.5 mm OD) porcine coronary arteries with use of in vitro tension recording. We also examined the effect of the dihydropyridine calcium channel agonist BAY K8644 on previously constricted epicardial porcine coronary artery segments in the presence of halothane or isoflurane. Our purpose was to determine (a) whether anesthetic effect on coronary arteries varied with arterial diameter, and (b) whether halothane and isoflurane inhibited BAY K8644-induced contraction of coronary vessels. Small and medium porcine coronary artery segments were constricted with K^+ (30 mM) and the resulting contraction was allowed to stabilize. This was followed by exposure to 0.5%, 1.0%, 2.0%, and 3.0% isoflurane or halothane and the resultant tension was again measured. Potassium-induced contractions were significantly relaxed by halothane in small coronary artery segments at 0.5%, 1.0%, 2.0%, and 3.0% and in medium coronary artery segments at 1.0%, 2.0%, and 3.0%. Potassium-induced contractions were significantly reduced by isoflurane only at 3.0% in both small and medium coronary artery segments. Halothane caused significantly more relaxation of both small and medium porcine coronary arteries previously constricted with K^+ (30 mM) than did isoflurane. There were no significant differences in coronary artery response to isoflurane or halothane with respect to coronary artery diameter. These experiments indicate that in porcine coronary arteries >0.5 mm OD, studied in vitro after K^+-induced contraction, isoflurane was not a potent coronary vasodilator. In another series of experiments, porcine epicardial coronary artery segments 1.5–2.0 mm OD were constricted with K^+ (30 mM) and then exposed to the highest concentration of anesthetic previously tested, namely, 3.0% isoflurane or halothane. BAY K8644 (3×10^{-7} M), a specific Ca^{2+} channel agonist, was then added in the presence of the K^+-induced contraction plus anesthetic and resultant tension was measured to determine the capacity of BAY K8644 to antagonize the anesthetic effect. Anesthetic was then removed from the K^+ (30 mM) solution and tension was remeasured in the presence of BAY K8644 alone. In the presence of halothane or isoflurane, the addition of BAY K8644 caused significant increases in contractile tension. The magnitude of the increased tension was not different from that seen in control (i.e., K^+ plus Ca^{2+} channel agonist) coronary artery segments exposed to BAY K8644 without the anesthetics. Three-percent halothane and isoflurane did not inhibit the ability of BAY K8644 (3×10^{-7} M) to cause contraction of porcine epicardial arteries previously constricted with K^+ (30 mM). We conclude that isoflurane is not a potent dilator of porcine coronary arteries in the size range 0.5–1.5 mm OD. We further conclude that neither 3% halothane nor isoflurane inhibits the coronary contraction induced by BAY K8644 (3×10^{-7} M).

(Anesth Analg 1992;75:9–17)

To determine the vasodilatory effect of halothane and isoflurane on porcine coronary arteries, we studied (a) the capacity of halothane and isoflurane to relax previously constricted coronary arteries as a function of vessel diameter, and (b) the capacity of both anesthetics to inhibit the effect of the dihydropyridine calcium agonist BAY K8644 on epicardial porcine coronary artery segments.

We have previously shown (1) that halothane relaxes preconstricted epicardial porcine coronary artery segments (1.5–2.0 mm outside diameter [OD]) more than isoflurane in vitro. In agreement with our in vitro porcine studies, Sill et al. (2) reported that isoflurane does not dilate large canine epicardial coronary vessels, although there were decreases in

Accepted for publication February 20, 1992.

This work was supported in part by the B. B. Sankey Research Award and Veterans Administration Research Advisory Group.

Address correspondence to Dr. Bollen, Department of Anesthesia, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

coronary vascular resistance, implying coronary dilation distal to large coronary arteries.

A variable response of coronary vessels to halothane and isoflurane as a function of vessel diameter would be expected from these findings, in that smaller vessels are perhaps more responsive to anesthetic-induced vasodilation than are larger vessels. We therefore compared the in vitro effects of isoflurane and halothane on preconstricted, functionally denervated arterial segments 0.5–1.0 mm OD (small) and 1.0–1.5 mm OD (medium) from porcine obtuse marginal and diagonal coronary artery branches.

The mechanisms by which anesthetics interfere with myocardial and vascular contractile tension are thought to involve effects on action potentials, extracellular Ca^{2+} entry, intracellular Ca^{2+} release, Ca^{2+} uptake, contractile proteins, and the vascular endothelium (3–15). To compare the capacity of halothane versus isoflurane to inhibit Ca^{2+} entry into vascular smooth muscle channels caused by BAY K8644, we also studied the capacity of BAY K8644 to further constrict porcine coronary artery segments previously constricted with K^+ (30 mM) in the presence of 3% halothane or isoflurane. BAY K8644 is a dihydropyridine calcium agonist (structurally related to nifedipine) that has been shown to activate voltage-sensitive Ca^{2+} channels, causing increased entry of external Ca^{2+}. We hypothesized that the increment of contraction caused by BAY K8644 would be inhibited by halothane and isoflurane. If so, we would then have evidence that the anesthetics may have a specific inhibitory effect on the Ca^{2+} channels and thus take steps toward further elucidating the mechanisms by which anesthetics produce vascular dilation.

Methods

Hearts from male and female pigs (weight 90–130 kg) were obtained from a local abattoir, as approved by the Stanford University Animal Research Committee. The hearts were removed within 5 min of slaughter and placed in cold (4°C) ionic solution for mammals (ISM) (mM composition: 130 NaCl, 16 $NaHCO_3$, 0.5 NaH_2PO_4, 4.7 KCl, 1.8 $CaCl_2$, 0.4 $MgCl_2$, 0.4 $MgSO_4$, 13 HEPES, and 5.5 dextrose; pH 7.4). The obtuse marginal branches of the circumflex artery and diagonal branches of the left anterior descending artery were dissected free to 0.5 mm OD with use of a dissecting microscope. Coronary artery ring segments 0.5–1.0 mm OD × 4 mm in length and 1.0–1.5 mm OD × 2.0 mm in length were mounted with stainless steel hooks in temperature-controlled, constant-flow muscle chambers. In separate experiments the left anterior descending coronary artery was dissected free with use of a dissecting microscope and 1-mm-long ring segments (1.5–2.0 mm OD) were prepared and mounted for use in BAY K8644 experiments. High-fidelity force transducers (Akers, Norway; sensitivity 1–9000 mg) were used for tension recording. The apparatus has been described previously (1).

Small- and Medium-Diameter Protocol

Muscle chambers were perfused with oxygenated (95% O_2–5% CO_2) ISM at 37°C. Arterial segments were stretched to obtain 1000 mg passive force and functionally denervated with 6-hydroxydopamine (16). This tension had previously been determined to provide the optimal length-tension relation. After a 1-h washout and stabilization period, coronary segments were constricted with K^+ (30 mM). After stabilization (plateau) of contraction, either halothane or isoflurane was added in incremental steps to equilibrate the solution bathing the blood vessels with 0.5%, 1.0%, 2.0%, and 3.0% vol/vol anesthetic, and tension was remeasured. Each anesthetic concentration was maintained for 15–20 min or until a stable new tension was obtained. After exposure to solution equilibrated with 3% anesthetic, the anesthetic was discontinued and the K^+-induced (30 mM) contraction allowed to increase until it plateaued again.

Up to eight coronary segments were studied at any given time. Only one anesthetic agent was studied per arterial segment. Each segment served as its internal control based on the return of the K^+-induced (30 mM) contraction after the 3% anesthetic increment was removed. Previous work (1) has documented the stability of this experimental preparation over time.

A total of 55 arterial segments from 10 pigs were studied. For each experiment, n refers to the number of pigs studied, not the number of vessels. For statistical analysis, results from all the arterial segments from the same pig studied under identical conditions were averaged to obtain mean values for each animal. Data for each group are presented as percent maximal tension of the original K^+-induced (30 mM) contracture. A repeated measure analysis of variance was used to analyze data. Single-tail t-tests when appropriate were used to obtain P values. The Bonferroni multiple-comparison procedure was used to maintain an overall significance level of $P < 0.05$.

BAY K8644 Protocol

Arterial segments 1.5–2.0 mm OD were stretched to obtain optimal passive tension of 1750 mg (1). Arterial segments were then constricted with K^+ (30 mM) and the contraction was allowed to plateau. After stabili-

Table 1. Anesthetic Effect on K^+ Contractile Tension in Porcine Small (0.5–1.0 mm OD) and Medium (1.0–1.5 mm OD) Coronary Artery Segments

	Percent maximal tension at anesthetic concentrations of 0%, 0.5%, 1.0%, 2.0%, and 3.0%				
	0	0.5	1.0	2.0	3.0
Halothane					
Medium (n = 8, 10 segments)	100	83.7 ± 7.4	72.5 ± 10.1[a]	50.5 ± 10.1[a,b]	26.1 ± 7.0[a,b]
Small (n = 10, 18 segments)	100	82.7 ± 6.3[a]	71.3 ± 7.6[a,b]	42.7 ± 8.3[a,b]	17.8 ± 5.8[a,b]
Isoflurane					
Medium (n = 6, 10 segments)	100	110.0 ± 7.8	111.3 ± 9.3	100.6 ± 10.3	80.6 ± 7.2[a]
Small (n = 9, 17 segments)	100	104.9 ± 6.3	106.2 ± 7.5	93.1 ± 8.1	70.2 ± 5.7[a]

Results are presented as percent ± SEM.
[a]Significantly different (actual, $P < 0.0125$) compared with 0%; overall $P < 0.05$ maintained by Bonferroni multiple-comparison procedure.
[b]Significantly different (actual, $P < 0.0063$) compared with isoflurane at the same concentration; overall $P < 0.05$ maintained by Bonferroni multiple-comparison procedure.

zation of K^+-induced contraction, either halothane or isoflurane was added to the bathing solution to achieve the equivalent of a 3% concentration, and the effect on tension was measured. After stabilization of anesthetic effect on the K^+-induced (30 mM) contraction, BAY K8644 (3×10^{-7} M) was added to the solution and the resultant contractile response was measured. After plateau of the BAY K8644 effect, anesthetic was removed from solution, and the effect of BAY K8644 without anesthetic was observed until stable. Parallel controls were performed wherein BAY K8644 was added to a K^+-induced (30 mM) contraction in the absence of any anesthetic, and the tension was measured. BAY K8644 (3×10^{-7} M) was studied based on literature indicating that this concentration of BAY K8644 causes maximal contraction of porcine coronary and rat femoral and aortic arteries (17–19).

Up to eight coronary artery segments were studied simultaneously. Seventy-two arterial segments from 10 additional pigs were studied (these animals were different from those used in the protocol studying small and medium arteries). For each experiment, n refers to the number of pigs studied, not the number of vessels. For statistical analysis, results from multiple arterial segments from each pig, studied under identical experimental conditions, were averaged to obtain mean values for each animal. Data for each group are presented as percentages of the maximal tension obtained with the initial K^+-induced (30 mM) contracture. Results are expressed as mean values ± SEM. An analysis of variance was used to analyze data. A P value < 0.05 was considered statistically significant. Because only one anesthetic concentration was studied, the Bonferroni multiple-comparison procedure was not used.

Anesthetic Analysis

Isoflurane or halothane was added to the solution as previously described (1). Ninety-five percent O_2–5% CO_2 flowing through calibrated anesthetic vaporizers was bubbled through ISM in special glass columns saturating the ISM with the appropriate percent of volatile anesthetic agent. The ISM, equilibrated with anesthetic, was then pumped to the muscle chambers through water-jacketed glass tubing with a peristaltic pump.

The apparatus was sealed to maintain appropriate anesthetic concentrations. For every experiment at each incremental anesthetic concentration, electron capture gas chromatographic measurement using heptane extraction was performed to document the actual anesthetic concentrations in the ISM bathing the arterial segments (1,20). Each perfusate sample was taken from the region immediately adjacent to the arterial segment under study. Targeted anesthetic concentrations in micrograms of anesthetic per milliliter of ISM were as follows: halothane 32, 64, 128, and 192; and isoflurane 21, 43, 86, and 128, respectively. Based on anesthetic solubility coefficients, these concentrations correspond to anesthetic concentrations for ISM at 37°C equilibrated with 0.5%, 1.0%, 2.0%, and 3.0% of the volatile agent, respectively (21). Anesthetic concentrations were always increased incrementally in the orders just described. Randomization of the order of anesthetic concentrations tested was not done because of our concern that prolonged effects from higher concentrations might influence results seen with lower concentrations (22).

Results

Variable-Diameter Protocol

Results are presented in Table 1 and Figures 1 and 2. In small (0.5–1.0 mm OD) coronary arteries previously constricted with K^+ (30 mM), halothane produced significant relaxation at 0.5%, 1.0%, 2.0%, and 3.0% concentrations ($P < 0.0125$). In medium (1.0–1.5 mm OD) coronary arteries, halothane pro-

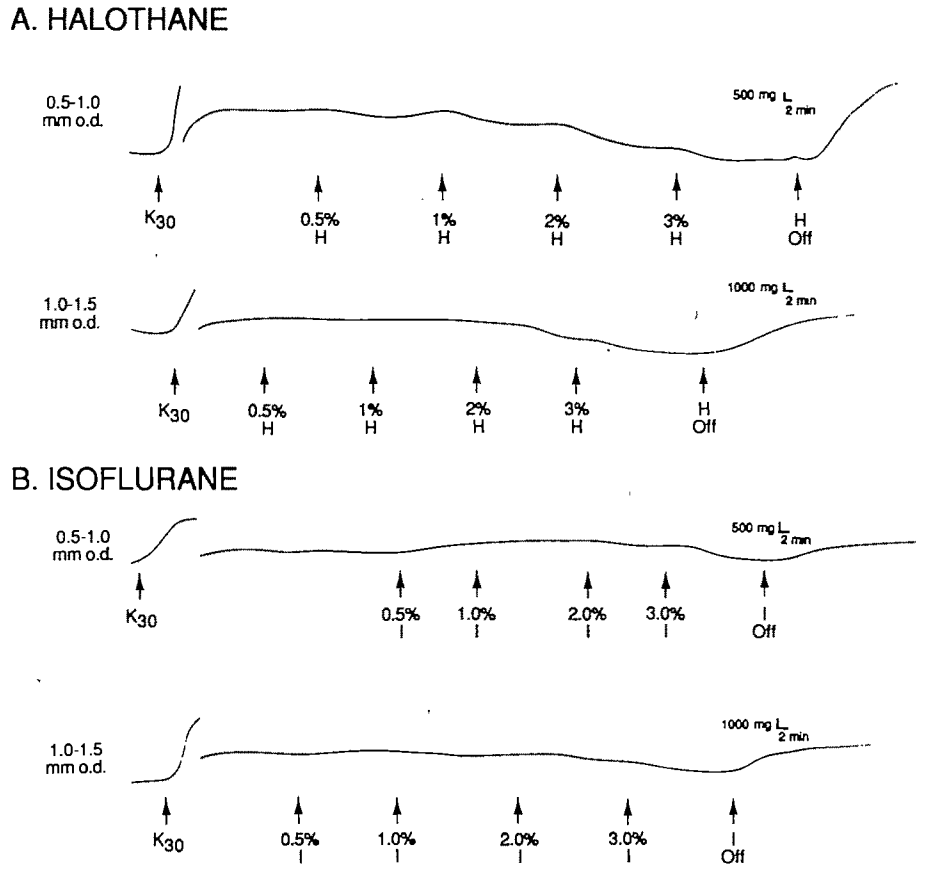


Figure 1. **A.** K^+-induced (30 mM) (K_{30}) sustained contraction of small (0.5–1.0 mm OD) and medium (1.0–1.5 mm OD) porcine coronary arteries relaxed by halothane (H) in a dose-dependent fashion. **B.** K^+-induced (30 mM) sustained contraction of small (0.5–1.0 mm OD) and medium (1.0–1.5 mm OD) porcine coronary arteries relaxed by isoflurane (I) only at 3.0% vol/vol.

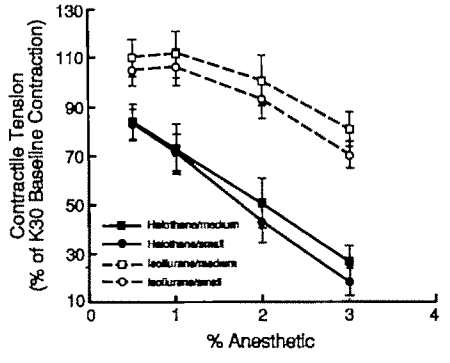


Figure 2. Relaxation of K^+-induced (30 mM) (K30) contraction in small (0.5–1.0 mm OD) and medium (1.0–1.5 mm OD) porcine coronary arteries exposed to halothane or isoflurane 0.5%, 1.0%, 2.0%, and 3.0% vol/vol occurring in a dose-dependent fashion.

duced significant relaxation of K^+-induced (30 mM) contractions at 1.0%, 2.0%, and 3.0% concentrations ($P < 0.0125$). There were no significant differences in coronary artery responses to halothane that were dependent on vessel diameter.

In small coronary arteries previously constricted with K^+ (30 mM), isoflurane caused significant relaxation only at the 3.0% concentration ($P < 0.0125$). Isoflurane in medium coronary arteries also caused significant relaxation only at 3.0% ($P < 0.0125$). There were no significant differences in coronary artery responses to isoflurane that were dependent on coronary artery diameter in the range tested.

In medium (1.0–1.5 mm OD) coronary arteries, halothane caused more relaxation of K^+-induced contractions than did isoflurane at the 2.0% and 3.0% concentrations ($P < 0.0063$). In small (0.5–1.0 mm OD) coronary arteries previously constricted with K^+, halothane caused more relaxation than did isoflurane at the 1.0%, 2.0%, and 3.0% concentrations ($P < 0.0063$).

BAY K8644 Protocol

Results are shown in Table 2 and Figure 3. In control experiments the addition of BAY K8644 to K^+-preconstricted coronary artery segments in the absence of halothane caused significant increases in contractile tension. The addition of (supraclinical) 3% halothane to K^+-preconstricted coronary artery seg-

Table 2. Effect of BAY K8644 on K^+-Induced Contraction in Porcine Coronary Artery Segments With and Without Anesthetic

	Percent maximal K^+-induced (30 mM) contraction				
	(A) K^+ (30 mM) contraction	(B) 3% Anesthetic added	(C) 3% Anesthetic BAY K8644	(D) Increase in contractile tension caused by BAY K8644 (C − B)	(E) BAY K8644 Postanesthetic
Halothane (n = 10, 20 segments)	100	31.3 ± 7.7	76.5 ± 7.7[a]	45.2[b]	141.3 ± 6.5[b]
Control (n = 10, 20 segments; no halothane)	100	103.2 ± 7.6	151.5 ± 7.8[c]	48.3	141.7 ± 6.7
Isoflurane (n = 9, 16 segments)	100	97.5 ± 3.6	154.8 ± 8.7[a]	57.3[b]	171.8 ± 10.0[b]
Control (n = 9, 16 segments; no isoflurane)	100	101.6 ± 4.6	147.4 ± 8.7[c]	45.3	145.4 ± 10.0

Results are presented as percent ± SEM.
[a]Significantly different compared with 3% anesthetic without BAY K8644 ($P < 0.05$).
[b]Not significantly different compared with control.
[c]Significantly different compared with control before BAY K8644 ($P < 0.05$).

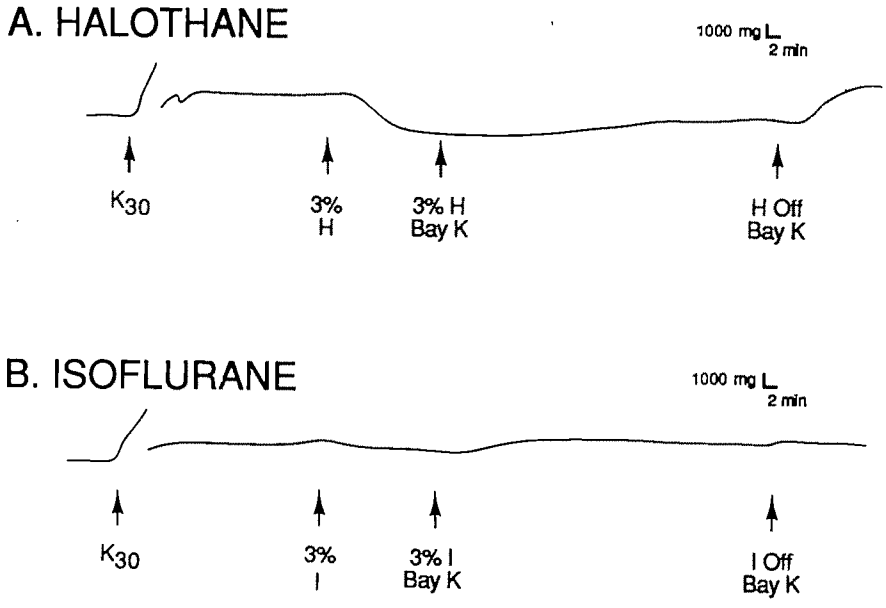


Figure 3. A. BAY K8644 (Bay K) added to K^+-induced (30 mM) (K_{30}) contraction of epicardial porcine coronary artery segments (1.5–2.0 mm OD) in the presence of 3% halothane (H). **B.** BAY K8644 added to K^+-induced (30 mM) contraction of epicardial porcine coronary artery segments (1.5–2.0 mm OD) in the presence of 3% isoflurane (I).

ments caused significant relaxation, which was partly reversed by the addition of BAY K8644. The magnitude of the BAY K8644-induced increased contraction in the presence of halothane was not statistically different from that seen by the addition of BAY K8644 in control experiments (halothane absent). After removing halothane from the BAY K8644-exposed segment, tension increased, resulting in a final tension that was not significantly different from the control segment exposed to BAY K8644 only.

In control experiments the addition of BAY K8644 to K^+-constricted coronary artery segments in the absence of isoflurane caused significant increases in contractile tension. The addition of isoflurane (3.0%) to coronary arteries previously constricted with K^+ (30 mM) did not significantly decrease contractile tension. The addition of BAY K8644 to K^+-contracted arteries exposed to 3% isoflurane caused a significant increase in contractile tension. The increase in tension by BAY K8644 in both control and isoflurane-exposed arterial segments was not significantly different. Removal of isoflurane from the BAY K8644-

exposed segments caused an increase in contractile tension. The final tension was not significantly different from that seen in the control arterial segments contracted with K^+ and exposed to BAY K8644 in the absence of isoflurane.

Anesthetic Concentration

Concentrations described earlier refer to target concentrations for anesthetic in ISM saturated with 0.5%, 1.0%, 2.0%, and 3.0% vol/vol of the volatile agent, respectively. Actual measured anesthetic concentrations (±SEM) in the bathing solutions for the halothane experiments correspond to 0.45% ± 0.02%, 1.02% ± 0.03%, 2.03% ± 0.08%, and 3.17% ± 0.12%. Concentrations for isoflurane correspond to 0.52% ± 0.015%, 0.98% ± 0.027%, 1.96% ± 0.07%, and 2.99% ± 0.09%.

Discussion

Our study examined the effect of isoflurane and halothane on previously constricted coronary vessels. The vessels studied were not epicardial but endocardial and are distal to large epicardial vessels but proximal to arterioles. Our findings show that halothane causes more relaxation than isoflurane in small (0.5–1.0 mm OD) and medium (1.0–1.5 mm OD) porcine coronary artery segments preconstricted with K^+ (30 mM). Although there appeared to be a tendency for both isoflurane and halothane to relax small arteries more than medium arteries, we could not demonstrate a significant effect of coronary artery diameter on the responses of coronary artery segments to isoflurane or halothane. These results are consistent with our previous work (1) in large porcine coronary arteries (1.5–2.0 mm OD), which reported that halothane relaxed K^+-constricted (30 mM) arteries more than did isoflurane.

Sill et al. (2) have shown isoflurane at concentrations of ≥1.5% to cause decreased coronary vascular resistance in intact dogs, implying coronary dilation. Our results are consistent with such a dose-related effect of isoflurane and halothane on the coronary circulation relative to clinical concentrations.

Large (2 mm OD) versus small (0.5 mm OD) canine coronary arteries have been shown to have variable responses to nitroglycerin and adenosine (23,24). Nitroglycerin caused greater relaxation of large vessels than small; adenosine caused greater relaxation of small vessels than large. We hypothesized that response to isoflurane and halothane would be variable as a function of arterial diameter in arteries 0.5–1.0 versus 1.0–1.5 mm OD. Although there appeared to be a tendency toward this, it was not statistically significant in the vessel diameters studied. Little effect with isoflurane was seen at concentrations of <3%, suggesting that at least in pigs, direct coronary vasodilating actions of isoflurane, if present, must be occurring in vessels of <0.5 mm OD. Research on distribution of coronary vascular resistance shows 75% of coronary vascular resistance to be distal to 0.2 mm OD (25,26). Isoflurane and halothane may be acting on coronary arteries of <0.5 mm OD.

In contrast, Hatano et al. (27) did report isoflurane and halothane to have differential effects in large versus small canine coronary arteries previously constricted with KCl. They found halothane-induced relaxation to be greater in large coronary arteries (>2.5 mm OD) than in distal smaller vessels (0.7–0.9 mm OD). They observed that relaxation by isoflurane was greater in small versus large coronary arteries. Our results show no significant isoflurane-induced relaxation of K^+-contracted (30 mM) porcine small, medium, or large coronary arteries at validated concentrations of <3.0% isoflurane (1). Further, our previous (1) and present results show that halothane consistently relaxes preconstricted coronary arteries more than equal concentrations of isoflurane in large, medium, and small porcine coronary arteries. This differs from the results that Hatano et al. (27) reported, which showed isoflurane to cause greater relaxation than halothane of KCl-induced contraction in small canine coronary arteries.

Differences between our findings in pigs and the Hatano et al. (27) findings in dogs may be explained by (a) different concentrations of the agents studied and (b) porcine versus canine preparation or (c) effective chemical denervation of the porcine preparation but not of the canine preparation.

It is common for anesthesiologists to refer to volatile anesthetic concentrations in MAC increments. We believe that because MAC refers to anesthetic potency as measured by gross motor responses (movement) to noxious stimuli and does not measure potency with respect to other physiologic parameters, including myocardial or vascular muscle depression, comparisons of equal concentrations of anesthetics, not MAC increments, were appropriate for these experiments. Hatano et al. (27) chose instead to compare MAC equivalents (1, 2, and 3 MAC) of isoflurane versus halothane (isoflurane 1.2%, 2.3%, 3.5% versus halothane 0.8%, 1.5%, 2.3%). At clinically relevant anesthetic concentrations, 1 MAC halothane versus 1 MAC isoflurane caused significantly greater relaxation in large canine coronary arteries with no significant difference in small coronary arteries. They did show isoflurane to cause greater relaxation of small versus large canine coronary arteries, becoming most apparent at 3 MAC (3.5% isoflurane versus 2.3% halothane).

There appear to be significant differences in the in

vitro responses of canine and porcine coronary artery segments to isoflurane and halothane (1, 13, 28). Blaise et al. (13) reported that isoflurane inhibits serotonin dose-response curves in both porcine and canine epicardial arteries but that the inhibition in canine and not in porcine coronary segments is endothelial dependent. In our protocol, coronary artery segments were chemically denervated to study the direct effects of halothane versus isoflurane. Muldoon et al. (29,30) showed that isoflurane and halothane inhibit norepinephrine release from vascular adrenergic nerve endings during sympathetic nerve stimulation. The effects of the anesthetics on adrenergic endings may explain some differences between our denervated porcine preparation and the Hatano et al. (27) nondenervated canine preparation, but this is not clear.

The complete mechanism of volatile anesthetic depression of cardiac and vascular contractile force remains unknown. Volatile agents do affect intracellular Ca^{2+} release, decrease intracellular Ca^{2+} accumulation in sarcoplasmic reticulum, and have some direct effect on contractile proteins (3–12). Halothane has been shown to depress slow cardiac action potentials in partially depolarized papillary muscle cells, an effect interpreted as depression of Ca^{2+} influx through slow channels (7–12). Bosnjak et al. (31) recently reported isoflurane, halothane, and enflurane to have similar concentration-dependent depressive effects on Ca^{2+} channel currents in canine ventricular cells.

To investigate the possible mechanisms for differences observed between halothane and isoflurane on coronary arteries in vitro, we studied the capacity of BAY K8644 to contract previously constricted porcine coronary arteries in the presence of 3% isoflurane or halothane. BAY K8644 is a dihydropyridine analogue that stimulates vascular contractions and augments cardiac twitch tension contraction. The effects of BAY K8644 have been shown to be mediated by activation of voltage-sensitive Ca^{2+} channels, increasing the influx of Ca^{2+} into the cell (32,33). BAY K8644 (3×10^{-7} M) was studied based on previously published work showing this concentration of BAY K8644 to cause maximal contraction of porcine coronary and rat femoral and aortic artery contraction.

The addition of BAY K8644 to coronary segments previously constricted by K^+ (30 mM) and exposed to halothane or isoflurane would be expected to contract the segments. This contraction should be influenced by (a) the capacity of the anesthetic to inhibit BAY K8644-enhanced Ca^{2+} entry through the BAY K8644 activation of potential-sensitive Ca^{2+} channels, or (b) the BAY K8644-mediated increase in intracellular Ca^{2+} acting to reverse anesthetic effect on intracellular contractile mechanisms, or both.

We found that BAY K8644-induced contraction in the presence of supraclinical 3% halothane or isoflurane was not significantly different from that seen in control vessels exposed to BAY K8644 without anesthetic (Table 2, column D). Halothane initially decreased K^+-induced contraction, which was then increased by the addition of BAY K8644. This increase was not significantly different from that observed in control experiments. Subsequent removal of halothane, with BAY K8644 remaining, resulted in increased contraction equal to the initial depression caused by halothane. Isoflurane caused no significant decrease in K^+-induced contraction, and the addition of BAY K8644 caused an increase in contraction not significantly different from control experiments.

These results are complex to interpret because of the multiple potential effects of the anesthetics on vascular smooth muscle. Possible interpretations could include (a) little effect of these agents on BAY K8644-activated channels, and (b) partial inhibition of BAY K8644-activated channels combined with partial reversal of intercellular effects of the anesthetics through Ca^{2+} entry enhanced by BAY K8644.

We had expected the inhibition of BAY K8644-induced contraction by isoflurane and halothane. This was not seen. Whether this reflects a difference between activation of Ca^{2+} channels by depolarization versus pharmacologic means is not known because Ca^{2+} currents have not been measured. Electrophysiologic techniques measuring the anesthetic effect on vascular smooth muscle ion fluxes will be required to clarify this question.

In the BAY K8644 protocol, 3% isoflurane did not relax the K^+-preconstricted coronary artery segment. This is different from the effect of 3% isoflurane observed in the other protocol but may be explained by a methodologic difference. In our other protocols, anesthetic was added in increments up to 3% over 1–1.5 h. In the BAY K8644 protocol, isoflurane or halothane was added only at 3%. The anesthetic dose-response curve method previously used may have had a cumulative effect, making the vessel relax more than when exposed to 3% anesthetic all at once. This is not uncommonly seen with contractile agonists when this in vitro preparation is used. Additionally, the BAY K8644 protocol vessels were not functionally denervated as they were in other porcine protocols.

Reversal of 3% halothane-induced relaxation of K^+-constricted arterial segments by BAY K8644 (3×10^{-7} M) was not complete. It is possible that a higher concentration of BAY K8644 may have caused more complete reversal of the anesthetic-induced relaxation; however, the concentration of BAY K8644 studied has previously been shown to maximally contract porcine coronary arteries. It is also possible

that the high concentration of BAY K8644 used may have masked inhibitory effects of isoflurane and halothane on the BAY K8644-activated channels.

The effects of isoflurane and halothane on the coronary circulation are clearly mediated by direct and indirect actions on the coronary arteries. Indirect effects on systemic hemodynamics, myocardial metabolism, and contractility have great effects on coronary blood flow. Larach et al. (34), using modified Langendorff isolated perfused rat hearts arrested with tetrodotoxin (a Na^+ channel blocker), have shown isoflurane and halothane to have equipotent direct vasodilating effects on coronary resistance vessels. Indirect effects of these agents must be considered when discussing their in vivo actions on the coronary circulation.

Concern about the clinical safety of isoflurane in patients with coronary artery disease was raised in 1983 when Reiz et al. (35) reported electrocardiographic (ECG) and lactate extraction signs of ischemia in 10 of 21 (47%) patients anesthetized with isoflurane undergoing major vascular surgery. In a subgroup of these patients (two of five who had ischemic changes), the ECG reverted to normal with normalization of coronary perfusion pressure and heart rate to awake values. In the remaining three patients in this subgroup, ECG changes consistent with ischemia persisted. Coronary blood flows were increased in these patients. The authors contended that isoflurane was a potent coronary dilator and that the observed ischemia was due to coronary steal.

Work done since then (36–42) has shown the incidence of ischemia in this patient population to range from 18% to 44% intraoperatively and to not always be associated with hemodynamic changes. Thus, the ECG changes observed by Reiz et al. (35) may not have been isoflurane induced but may have been more a reflection of the ongoing coronary artery disease process in this patient population.

The present study showing halothane to cause greater in vitro relaxation of small and medium coronary artery segments than isoflurane adds to our knowledge of the effects of these agents on the coronary circulation. Isoflurane in vitro appears not to be a potent coronary artery dilator at clinically relevant concentrations. This is supported by the work of Hatano et al. (27), where concentrations >1 MAC were needed for significant effects to be seen. Our experiments were performed on coronary vessels of >0.5 mm OD and may not necessarily apply to smaller vessels. Recent research (25,26) on distribution of coronary vascular resistance shows 75% of coronary vascular resistance to be distal to 0.2 mm OD. Isoflurane (and halothane) may act primarily on coronary arteries with less than the 0.5 mm OD we tested. Although this is possible, the report by Sill et al. (2) concluded that isoflurane-treated coronary arterioles in the intact dog showed no decreases in coronary vascular resistance at concentrations <1.5 MAC. Thus, it appears that at the small artery and microcirculatory levels, isoflurane at clinically relevant concentrations is not a potent coronary dilator. Certainly, isoflurane and halothane are not as potent as nitroglycerin and adenosine in relaxing coronary arteries. This has been shown by Hatano et al. (27) in vitro and Hickey et al. (43) in vivo in dogs.

Under special conditions, avoided in clinical situations, isoflurane has been shown to cause coronary steal in dogs with (a) collateral coronary anatomy, (b) 1.2%–1.5% MAC isoflurane, and (c) coronary perfusion pressure decreased to the point where wall motion abnormalities are present (44). Results of recent large-outcome studies (45–48) showing that choice of anesthetic technique does not influence outcome would suggest that animal studies showing isoflurane-associated steal under special conditions are not applicable to the clinical situation.

We conclude that halothane caused greater relaxation than isoflurane of small (0.5–1.0 mm OD) and medium (1.0–1.5 mm OD) functionally denervated porcine coronary artery segments previously constricted with K^+ (30 mM). In the preparation studied, there was no variable response to isoflurane or halothane based on vessel diameter. Isoflurane at clinically relevant concentrations was not able to relax preconstricted coronary arteries. We further conclude that neither halothane nor isoflurane, in supraclinical concentrations (3%), was able to inhibit coronary artery contraction induced by BAY K8644 (3×10^{-7} M).

References

1. Bollen BA, Tinker JH, Hermsmeyer K. Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 1987;66:748–52.
2. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. Anesthesiology 1987;66:273–9.
3. Su J, Bell J. Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit. Anesth Analg 1986;65:457–67.
4. Su JY, Zhang CC. Intracellular mechanisms of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 1989;71:409–17.
5. Lynch C. Are volatile anesthetic agents really calcium entry blockers? Anesthesiology 1984;61:644–6.
6. Lynch C, Vogel S, Pratila MG, Sperelakis N. Enflurane depression of myocardial slow action potentials. J Pharmacol Exp Ther 1982;222:405–9.
7. Lynch C. Differential depression of myocardial contractility by halothane and isoflurane in vitro. Anesthesiology 1986;64:620–31.
8. Katsuoka M, Kobayashi K, Ohnishi T. Volatile anesthetics decrease calcium content of isolated myocytes. Anesthesiology 1989;70:954–60.
9. Murat I, Ventura-Clapier R, Vassort G. Halothane, enflurane,

and isoflurane decrease calcium sensitivity and maximal force in detergent-treated rat cardiac fibers. Anesthesiology 1988;69: 892–9.
10. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: a review of possible mechanisms. Anesthesiology 1987;67:745–66.
11. Porsius AJ, Van Zwieten PA. Influence of halothane on calcium movement in isolated heart muscle and in isolated plasma membranes. Arch Int Pharmacodyn 1975;218:29–39.
12. Bosnjak ZJ, Kampine JP. Effects of halothane on transmembrane potentials, Ca^{2+} transients and papillary muscle tension in the cat. Am J Physiol 1986;251:H374–81.
13. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
14. Stone DJ, Johns RA. Endothelium-dependent effects of halothane, enflurane, and isoflurane on isolated rat aortic vascular rings. Anesthesiology 1989;71:126–32.
15. Muldoon SM, Hart JL, Bowen KA, Freas W. Attenuation of endothelium-mediated vasodilation by halothane. Anesthesiology 1988;68:31–7.
16. Aprigliano O, Hermsmeyer K. In vitro denervation of portal vein and caudal artery of the rat. J Pharmacol Exp Ther 1976;198:568–77.
17. Dubé GP, Yung HB, Schwartz A. Effects of a novel calcium channel agonist dihydropyridine analogue, Bay K 8644, on pig coronary artery: biphasic mechanical response and paradoxical potentiation of contraction by diltiazem and nimodipine. J Cardiovasc Pharmacol 1985;7:377–89.
18. Mikkelsen EO, Nyborg NCB. Comparison of the effects of the vasoconstrictive dihydropyridines Bay K 8644 and CGP 28392 on isolated rat aorta: different sensitivities to ultraviolet radiation. J Cardiovasc Pharmacol 1986;8:476–82.
19. Aoki K, Asano M. Effects of Bay K 8644 and nifedipine on femoral arteries of spontaneously hypertensive rats. Br J Pharmacol 1986;88:221–30.
20. Davis D. A method of gas chromatography using electron capture detection for the determination of blood concentration of halothane, chloroform and trichloroethylene. Br J Anaesth 1978;50:147–55.
21. Lerman J, Willis M, Gregory G, Eger E. Osmolarity determines the solubility of anesthetics in aqueous solutions at 37°C. Anesthesiology 1983;59:554–8.
22. Spiss C, Smith C, Tsujimoto G, Hoffman B, Maze M. Prolonged hyporesponsiveness of vascular smooth muscle contraction after halothane anesthesia in rabbits. Anesth Analg 1985;64:1–6.
23. Fam WM, McGregor M. Effect of nitroglycerin and dipyridamole on regional coronary resistance. Circ Res 1968;22:649–59.
24. Schnaar RL, Sparks HV. Response of large and small coronary arteries to nitroglycerin, $NaNO_2$, and adenosine. Am J Physiol 1972;223:223–8.
25. Marcus ML, Chilian WM, Kanatsuka H, Dellsperger KC, Easthma CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. Circulation 1990;82:1–7.
26. Chilian WM, Eastham CL, Marcus ML. Microvascular distribution of coronary vascular resistance in beating left ventricle. Am J Physiol 1986;251:H779–88.
27. Hatano Y, Nakamura K, Yakushiji T, Nishiwada M, Mori K. Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. Anesthesiology 1990;73:513–7.
28. Witzeling TM, Sill JC, Hughes JM, Blaise GA, Nugent M, Rorie DK. Isoflurane and halothane attenuate coronary artery constriction evoked by serotonin in isolated porcine vessels and in intact pigs. Anesthesiology 1990;73:100–8.
29. Muldoon SM, Vanhoutte PM, Lorenz RR, Van Dyke RA. Venomotor changes caused by halothane acting on the sympathetic nerves. Anesthesiology 1975;43:41–8.
30. Edwards TL, Freas W, McGehee J, Muldoon SM. Mechanism of vasomotor changes with isoflurane (abstract). Anesth Analg 1988;67:S56.
31. Bosnjak ZJ, Supan FD, Rusch NJ. The effects of halothane, enflurane, and isoflurane on calcium currents in isolated canine ventricular cells. Anesthesiology 1991;74:340–5.
32. Yamamoto H, Hwang OK, Van Breemen C. BAY K8644 differentiates between potential and receptor operated Ca^{++} channels. Eur J Pharmacol 1984;102:555–7.
33. Hwang KS, Van Breemen C. Effects of the Ca agonist BAY K8644 on 45 Ca influx and net Ca uptake into rabbit aortic smooth muscle. Eur J Pharmacol 1985;116:299–305.
34. Larach DR, Schuler HG, Skeehan TM, Peterson CJ. Direct effects of myocardial depressant drugs on coronary vascular tone: anesthetic vasodilation by halothane and isoflurane. J Pharmacol Exp Ther 1990;254:58–64.
35. Reiz S, Balfors E, Sorensen M, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.
36. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
37. Knight AA, Hollenberg M, London M, et al. Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 1988;68:661–8.
38. London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. Anesthesiology 1988;69:232–41.
39. Leung JM, O'Kelly B, Browner WS, et al. Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1989;71:16–25.
40. London MJ, Tubau JF, Wong MG, et al. The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. Anesthesiology 1990;73:644–55.
41. Slogoff S, Keats AS, David Y, Igo SR. Incidence of perioperative myocardial ischemia detected by different electrocardiographic systems. Anesthesiology 1990;73:1074–81.
42. Smith RC, Leung JM, Mangano DT, and the SPI Research Group. Postoperative myocardial ischemia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1991;74:464–73.
43. Hickey RF, Sybert PE, Verrier ED, Cason BA. Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 1988;68:21–30.
44. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.
45. Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989;70:179–88.
46. Tuman KJ, McCarthy RJ, Spiess BD, DaValle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 1989;70:189–98.
47. Inoue K, Reichelt W, El-Banayosy A, et al. Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? Anesth Analg 1990;71:469–74.
48. Slogoff S, Keats AS, Dear WE, et al. Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. Anesth Analg 1991;72:22–7.

Mechanisms of Renal Hemodynamic Impairment During Infrarenal Aortic Cross-Clamping

Pascal Colson, MD, Jean Ribstein, MD, Jacques R. Séguin, MD, Charles Marty-Ane, MD, and Bernard Roquefeuil, MD

Departments of Anesthesiology and Cardiovascular Surgery, Hôpital Saint-Eloi and Physiology Laboratory, Institut de Biologie, Centre Hospitalo-Universitaire, Montpellier, France

Infrarenal aortic cross-clamping is associated with impairment of renal hemodynamics due to vasoconstriction, the mechanism of which remains under debate. To assess the renal effect of two potent renal vasodilators (enalapril, a converting enzyme inhibitor, and nicardipine, a calcium antagonist), 24 patients scheduled for reconstructive aortic surgery were randomly allocated to one of three treatment groups ($n = 8$ each) and received either a placebo, nicardipine, or enalapril. Anesthesia consisted of flunitrazepam, fentanyl, pancuronium, and, occasionally, droperidol. Although aortic cross-clamping was associated with no change in mean arterial blood pressure, decreased cardiac output and increased systemic vascular resistance occurred in control patients (33% and 43%, respectively, both $P < 0.05$ versus baseline) and nicardipine-treated patients (51.7% and 67.7%, respectively, both $P < 0.05$ versus baseline); however, changes in cardiac output and systemic vascular resistance failed to reach significance in enalapril-treated patients. Glomerular filtration rate (technetium 99–diethylenetriaminepentaacetic acid clearance) and effective renal plasma flow (iodo-Hippuran 131 clearance) decreased for the duration of aortic cross-clamping in control patients (42.9% and 18.5%, respectively, both $P < 0.05$ versus baseline) and enalapril-treated patients (34.0% and 38.1%, respectively, both $P < 0.05$ versus baseline), but no change was observed in nicardipine-treated patients. These results suggest that the renin-angiotensin system is not an important determinant of the renal vasoconstriction associated with aortic cross-clamping. In contrast, renal dysfunction may be alleviated by the dihydropyridine derivative nicardipine, which probably acts at the level of the preglomerular resistance vessels.

(Anesth Analg 1992;75:18–23)

Cross-clamping of the infrarenal aorta, as required for abdominal aortic reconstructive surgery, is associated with well-documented alterations in systemic hemodynamics, namely, decreased cardiac output and increased systemic vascular resistance (1–3). A consistent reduction in renal plasma flow and a decrease in glomerular filtration rate (GFR), attributed to renal vasoconstriction, have also been observed during and after aortic cross-clamping (4), but the underlying mechanisms are not understood (5). Nevertheless, postoperative acute renal failure, the most frequent complication after aortic reconstruction (6,7), may result, at least in part, from these alterations in renal hemodynamics (4,5).

Converting enzyme inhibitors (CEIs) are pharmacologic blockers of the renin-angiotensin system and can improve renal circulation when the renin-angiotensin system is activated (8,9). Because plasma renin activity has been found to be increased during aortic cross-clamping (10,11), it is conceivable that CEI administration could blunt the renal hemodynamic changes associated with abdominal aortic surgery. On the other hand, calcium antagonists (long-lasting voltage-operated channel antagonists) decrease renal response to different vasoconstrictor agents (12,13) and have attenuated renal failure in various experimental (14,15) and some clinical (16) studies.

The purpose of this study was thus to assess the effect of enalapril, a CEI, and nicardipine, a calcium antagonist, on renal hemodynamics during infrarenal aortic surgery.

Methods

The study population comprised 24 patients (23 men and 1 woman, aged 40–73 yr) scheduled for infrarenal

Accepted for publication March 4, 1992.

Address correspondence to Dr. Colson, Departement d'Anesthesie, Centre Hospitalo-Universitaire, Hôpital Saint-Eloi, 34059 Montpellier, France.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

aortic surgery because of aortic aneurysm (n = 8) or aortoocclusive disease (n = 16). Patients with previous renal dysfunction (serum creatinine >1.8 mg/dL), cardiac failure, aortic thrombosis, long-term treatment with calcium antagonists or CEIs, or who had undergone emergency surgery were not included. No renal artery stenosis was detectable on angiography. Preoperative therapy (nitrates, n = 4; methyldopa, n = 1) was maintained until day of surgery, but diuretics (n = 3) were withdrawn 4 days before surgery. The protocol was approved by the Committee for Ethics in Clinical Research of our institution, and informed consent was obtained from each patient.

Two days before surgery, patients were allocated to one of three groups in randomized, double-blind fashion: control group (CTL, n = 8), nicardipine group (NIC, n = 8), enalapril group (ENA, n = 8). The ENA group received enalapril (10 mg twice daily), whereas the CTL and NIC groups received a placebo (1 tablet twice daily). The last dose of either enalapril or placebo was given at the time of preanesthetic medication, approximately 2 h before surgery. Both treatments were well tolerated. At skin incision, nicardipine was administered to the NIC group (2-mg IV bolus injection, then 2 mg/h), and placebo (5% glucose solution) was infused in patients in both of the other groups.

In all patients, a peripheral vein was cannulated before anesthesia, then a 7F thermodilution pulmonary catheter was inserted through the internal jugular vein; a radial artery catheter and a Foley urinary bladder catheter were inserted after the induction of anesthesia. The aorta was approached by means of a median laparotomy.

Preanesthetic medication consisted of flunitrazepam (1 mg orally). Anesthesia was induced and maintained with fentanyl (0.006 mg/kg, then 0.006 $mg \cdot kg^{-1} \cdot h^{-1}$), flunitrazepam (0.03 mg/kg), and pancuronium (0.1 mg/kg). Ventilation was controlled with 50% nitrous oxide and oxygen to ensure normal arterial blood gases.

When mean arterial blood pressure (MAP) exceeded 105 mm Hg, additional doses of fentanyl (0.1 or 0.2 mg) and droperidol (2.5-mg bolus injection, repeated if necessary) were added. Intravenous fluid (crystalloid, colloid, or blood) was infused to maintain MAP, pulmonary capillary wedge pressure (PCWP), and hematocrit above 60 mm Hg, 8 mm Hg, and 28%, respectively.

Systemic and renal hemodynamics were measured at three time periods, as follows: after induction of anesthesia and during surgical approach to the aorta (preclamp period), during aortic cross-clamping (periclamp period), and after declamping and distal revascularization (postclamp period). Heart rate, MAP, PCWP, and cardiac output were recorded and blood samples withdrawn at the midpoint of each clearance period (20–30 min each). Glomerular filtration rate and effective renal plasma flow (ERPF) were estimated from clearance of technetium 99–diethylenetriaminepenta-acetic acid (DTPA) and iodo-Hippuran 131, respectively, with the continuous infusion technique described for this laboratory (9,17). Fractional sodium excretion was calculated as sodium clearance/DTPA clearance × 100, where clearance was calculated as urinary concentration × urinary output/plasma concentration.

Data are expressed as mean values ± SEM. Two-way repeated measures analysis of variance and Student's t-test with Bonferroni's correction were used to assess significance between and within groups. A P value <0.05 was considered to be the minimal level of significance.

Results

Baseline Variables

As shown in Table 1, the three groups were similar with regard to clinical characteristics, preoperative serum creatinine, and arterial pressure. Overall, induction of anesthesia was followed by a consistent but limited (no vasopressor was given in any group) decrease in arterial pressure in the three groups. This change was more marked in the ENA group ($P < 0.05$ versus both NIC and CTL groups). During the initial phase of operation (from induction of anesthesia to skin incision), less volume infusion was required to maintain MAP in the NIC group ($P < 0.05$ versus both ENA and CTL groups). However, volume infusion requirements for the entire procedure were not different, and hematocrits were similar, in the three groups at any time during surgery. Of note, the CTL group, and to a lesser extent the ENA but not the NIC group, required droperidol. In addition, no bradycardia (heart rate <40 beats/min) was observed in any group.

Effect of Aortic Cross-Clamping on Systemic Hemodynamics

During the preclamp period, systemic hemodynamic variables (Table 2) were similar in the three groups, except for heart rate, which was higher in the NIC group ($P < 0.05$ versus CTL group). During aortic cross-clamping, MAP and PCWP were not significantly altered in any group. Cardiac output decreased significantly in the CTL and NIC groups (33% and 43%, respectively, both $P < 0.05$ versus baseline) and only to a moderate extent (−9%, P = NS) in the ENA group. In fact, calculated stroke volume and stroke

Table 1. Clinical Characteristics and Perioperative Data for 24 Patients in the Three Study Groups

	Study group			
	Control (n = 8)	Nicardipine (n = 8)	Enalapril (n = 8)	P value
Clinical				
Age (yr)	63 ± 1	63 ± 3	58 ± 4	
Weight (kg)	70.4 ± 1.9	65.9 ± 2.3	70.3 ± 5.7	
Serum creatinine (mg/dL)	1.37 ± 0.07	1.39 ± 0.06	1.52 ± 0.11	
MAP (mm Hg)	86.0 ± 6.9	93.7 ± 1.7	86.7 ± 7.4	
Surgical				
Aortoocclusive disease/aortic aneurysms	4/4	5/3	7/1	
Clamping time (min)	37.9 ± 4.1	40.4 ± 2.9	44.1 ± 8.3	
Anesthesia				
Fentanyl (μg/h)	6.7 ± 0.4	6.4 ± 0.1	7.1 ± 0.5	
Droperidol (mg/kg)	0.28 ± 0.01	0	0.13 ± 0.04	[a,b,c]
MAP_{min} (mm Hg)	72.1 ± 4.7	78.6 ± 4.6	61.5 ± 3.0	[a,c]
Vol_{ini} (L)	1.03 ± 0.1	0.47 ± 0.12	0.84 ± 0.1	[a,b]
Vol_{tot} (L/h)	1.22 ± 0.08	0.99 ± 0.1	1.10 ± 0.07	

MAP, mean arterial blood pressure; MAP_{min}, lowest MAP after induction of anesthesia; Vol_{ini}, volume injected initially (from induction to surgical incision); Vol_{tot}, total volume infused (per hour of surgery).
Data are expressed as mean values ± SEM.
[a] $P < 0.05$ nicardipine-treated versus enalapril-treated patients.
[b] $P < 0.05$ controls versus nicardipine-treated patients.
[c] $P < 0.05$ control group versus enalapril-treated patients.

volume index decreased uniformly in all three groups (data not shown). Systemic vascular resistance increased in the CTL and NIC groups but not in the ENA group.

Clamp removal was followed by no further change in MAP and PCWP, but heart rate increased in the ENA and NIC groups. After declamping, cardiac output increased, whereas systemic vascular resistance decreased in the CTL and NIC groups but without reaching preclamp values.

Effect of Aortic Cross-Clamping on Renal Hemodynamics

As shown in Table 3, renal variables were similar in the three groups during the preclamp period, except for absolute and fractional excretion of sodium, which were significantly higher in the NIC group. During clamping, both ERPF and GFR decreased in the CTL and ENA groups (all $P < 0.05$ versus baseline). Both ERPF and GFR were maintained in the NIC group (both $P < 0.05$ versus CTL group). Fraction of cardiac output delivered to the kidneys (renal blood flow/cardiac output ratio) increased only in the NIC group (data not shown).

After aortic declamping, changes in renal variables reversed in the CTL and ENA groups, but GFR remained lower than preclamp values in both groups. In the NIC group, ERPF but not GFR was moderately altered (Table 3); thus, calculated filtration fraction was significantly higher than in both of the other groups (28.7% ± 1.8% versus 20.8% ± 2.5% and 18.8% ± 1.2% in the CTL and ENA groups, respectively; $P < 0.05$).

Postoperative Course

Arterial pressure returned to preoperative values within 24 h. No instance of acute renal failure occurred postoperatively in any group. On the first postoperative day, mean blood urea nitrogen was 2.8 ± 0.5, 2.5 ± 0.5, and 3.3 ± 0.5 in the CTL, NIC, and ENA groups, respectively (P = NS).

Discussion

The present studies, conducted in patients with supposed euvolemia and no major cardiovascular impairment, confirm that infrarenal aortic cross-clamping is associated with consistent changes in cardiac output and systemic vascular resistance as well as significant decreases in renal blood flow and GFR. Short-term treatment with the CEI enalapril attenuated the acute aortic cross-clamping-induced changes in systemic but not renal hemodynamics. Continuous infusion of the calcium antagonist nicardipine resulted in improved stability of systemic hemodynamics during surgery and diminished the transient aortic cross-clamping-associated renal hemodynamic alteration.

Table 2. Systemic Hemodynamic Variables in the Three Study Groups

	Study group			
	Control	Nicardipine	Enalapril	*P* value
HR (beats/min)				
Preclamp	69.0 ± 5.1	85.9 ± 2.4	77.5 ± 4.9	[b]
Periclamp	60.4 ± 3.3[a]	75.5 ± 6.2[a]	66.3 ± 4.0[a]	[b]
Postclamp	61.1 ± 4.3	83.5 ± 7.0[a]	75.1 ± 3.7	[b]
MAP (mm Hg)				
Preclamp	85.4 ± 4.1	89.9 ± 2.4	82.3 ± 1.7	
Periclamp	84.4 ± 3.4	86.4 ± 3.7	84.1 ± 2.8	
Postclamp	84.9 ± 5.0	83.9 ± 3.1[a]	87.5 ± 3.7	
PCWP (mm Hg)				
Preclamp	11.6 ± 1.6	13.3 ± 1.4	14.0 ± 1.0	
Periclamp	10.1 ± 1.3	13.2 ± 1.0	12.0 ± 1.1	
Postclamp	9.4 ± 1.5	12.2 ± 2.0	13.0 ± 1.5	
CO (L/min)				
Preclamp	7.6 ± 0.7	8.2 ± 0.6	6.5 ± 0.9	
Periclamp	5.1 ± 0.4[a]	4.5 ± 0.3[a]	5.2 ± 0.4	
Postclamp	5.6 ± 0.4[a]	6.8 ± 0.5	6.0 ± 0.4	
SVR (dyne·s·cm^{-5})				
Preclamp	870 ± 109	860 ± 67	1020 ± 96	
Periclamp	1320 ± 156[a]	1440 ± 150[a]	1212 ± 90	
Postclamp	1180 ± 154	950 ± 75	1110 ± 90	

HR, heart rate; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistances; Preclamp, period from induction of anesthesia to skin incision; Periclamp, period during aortic cross-clamping; Postclamp, period after declamping and distal revascularization.

Data are expressed as mean values ± SEM.

[a] $P < 0.05$ versus preclamp values.

[b] $P < 0.05$ controls versus nicardipine-treated patients.

Arterial Pressure and Systemic Hemodynamics

Angiotensin-CEIs have proved beneficial and are increasingly used in the treatment of hypertensive disease and congestive heart failure. One view holds that CEI treatment may have deleterious effects at time of anesthesia (18). Actually, arterial blood pressure decreased more in enalapril-treated patients than in the other subjects after induction of anesthesia, but this decrease was moderate and transient. These results agree with our previous studies (9,19) but differ from those of Kataja et al. (20). Although accurate biological assessment of renin-angiotensin system blockade was not available in this study, there is no doubt that the large doses of enalapril used effectively suppressed circulating angiotensin II at the time of surgery (21). The discrepancies could perhaps be accounted for, at least in part, by differences in patient volume status. It is recognized that arterial pressure of CEI-treated patients is markedly volume dependent (22), and thus low PCWP at induction of anesthesia (20) represents an early warning of a higher risk of falling arterial pressure.

Hemodynamic variations before and during clamping were almost identical in control and nicardipine-treated patients and were closely compared with other studies (1,4,5,20,23). Most authors agree on the existence of decreased cardiac output and increased calculated vascular resistances during aortic cross-clamping, whatever anesthetic is used (23), even though magnitudes of reported changes vary widely. Gelman et al. (3) hypothesized that the decrease in cardiac output may reflect a metabolic and hemodynamic adaptation to the exclusion of lower body rather than a deterioration in cardiac performance. In the present study, hemodynamic changes were less marked in the enalapril-treated group. Most of these patients had aortoiliac occlusive disease, which might have minimized the effect of clamping on systemic hemodynamics (24). However, renal impairment during aortic cross-clamping was comparable in control and enalapril-treated patients, a finding compatible with the idea that alteration in systemic hemodynamics is not an important factor in the genesis of renal vasoconstriction.

Renal Hemodynamics

At present, few studies have reported on renal hemodynamics during aortic cross-clamping (4,5,23,25). Based on these data, renal vasoconstriction appears to mediate the observed decrease in renal blood flow and GFR during aortic cross-clamping (4,5), but its pathophysiology is unknown. Evidence against a role of increased sympathetic renal activity derives from

P 94 539

Table 3. Renal Hemodynamics

	Study group			
	Control	Nicardipine	Enalapril	*P* value
ERPF ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)				
Preclamp	227 ± 62	336 ± 90	433 ± 193	
Periclamp	185 ± 45[a]	352 ± 65	268 ± 62[a]	[b]
Postclamp	317 ± 61	260 ± 43	353 ± 52	
GFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)				
Preclamp	71.4 ± 12.5	63.2 ± 11.0	74.4 ± 15.3	
Periclamp	40.8 ± 8.5[a]	78.9 ± 14.3	49.1 ± 10.7[a]	[b]
Postclamp	59.6 ± 9.0[a]	71.6 ± 10.0	64.0 ± 7.4[a]	
Urine flow (mL/min)				
Preclamp	2.0 ± 0.8	1.9 ± 0.5	1.0 ± 0.2	
Periclamp	0.6 ± 0.1	1.6 ± 0.6	0.7 ± 0.1	
Postclamp	0.7 ± 0.1	2.5 ± 1	0.8 ± 0.1	[b]
UNaV ($mmol \cdot L^{-1} \cdot min^{-1}$)				
Preclamp	28.6 ± 9	105.3 ± 28.8	21.4 ± 4.5	[b,c]
Periclamp	15.2 ± 3	118.5 ± 74.4	41.0 ± 11.0	[b,d]
Postclamp	37.6 ± 7.8	226.8 ± 130.7	45.0 ± 10.4[a]	
Fe_{Na} (%)				
Preclamp	0.24 ± 0.05	0.76 ± 0.21	0.34 ± 0.08	[b]
Periclamp	0.28 ± 0.06	0.86 ± 0.25	0.56 ± 0.15[a]	[b]
Postclamp	0.55 ± 0.11[a]	1.16 ± 0.35	0.64 ± 0.14[a]	

ERPF, effective renal plasma flow (Hippuran clearance); GFR, glomerular filtration rate (DTPA clearance); UNaV, urinary sodium excretion; Fe_{Na}, fractional sodium excretion. (See Table 2 for explanation of Pre-, Peri-, and Postclamp.)

Data are expressed as mean values ± SEM.

[a] $P < 0.05$ versus preclamp values.

[b] $P < 0.05$ control group versus nicardipine-treated patients.

[c] $P < 0.05$ nicardipine-treated versus enalapril-treated patients.

[d] $P < 0.05$ control group versus enalapril-treated patients.

studies showing that epidural anesthesia or droperidol-fentanyl anesthesia, which both maintained renal hemodynamics before aortic cross-clamping, failed to alter aortic cross-clamping-induced changes in renal hemodynamics (5,23). Participation of the renin-angiotensin system was suspected because plasma renin activity was found to be increased during aortic cross-clamping (20,25). However, extracellular fluid volume expansion, which is known to reduce renin dependency of arterial pressure and renal function (22), failed to prevent perioperative renal impairment during infrarenal aortic surgery (25). Our results, showing that CEI pretreatment does not attenuate decreased renal blood flow and GFR without renal artery stenosis and with a rather stable cardiac output, further suggest that activation of the renin-angiotensin system plays at most a minor role in aortic cross-clamping-associated renal alteration.

An important finding of this study is that nicardipine treatment prevented renal hemodynamic impairment during aortic cross-clamping. Mannitol, for example, was shown to preserve renal perfusion during infrarenal aortic cross-clamping in animals (26) but not GFR in humans (25), despite a significant increase in cardiac index. Renal preservation cannot be attributed to a beneficial effect of nicardipine on systemic hemodynamics because neither arterial pressure nor cardiac output differed from control patients. It thus appears that calcium antagonists act at the renal level to alleviate aortic cross-clamping-induced renal hemodynamic alteration. The exact mechanism of this beneficial effect remains to be defined. It could relate to the previously known (27) and presently observed natriuretic effect of nicardipine. Nonetheless, in previous studies mannitol-induced natriuresis was not associated with significant alterations of aortic cross-clamping-induced decreases in GFR (25). Second, experimental studies based on videomicroscopic as well as clearance and micropuncture methods have demonstrated that calcium antagonists (including nicardipine) may improve compromised renal circulation and augment GFR because of preferential effect at the afferent arteriole (12). Specifically, blockade of voltage-operated calcium channels may have attenuated a myogenic response (28,29) of small arterioles through inhibition of a stretch-dependent ion channel (29). Alternatively, the dihydropyridine derivative may have blunted the vasoconstrictive effect of endopeptides such as endothelin (30), a putative mediator of acute renal failure (31). The calcium antagonist effect of isoflurane, which is comparable to the dihydropyridine derivative (32), might account for the bene-

ficial effect of isoflurane during aortic cross-clamping (23).

Although it is not known whether blunting of intraoperative changes in renal hemodynamics associated with aortic clamping and declamping might prevent perioperative renal dysfunction, we believe that intrarenal vasodilation could help preserve renal function during infrarenal aortic surgery. Further studies are required in patients at high risk for developing renal failure during aortic surgery to assess a possible renal protective effect of nicardipine.

References

1. Silverstein PR, Caldera DL, Cullen DJ, Davison JK, Darling RC, Emerson CW. Avoiding the hemodynamic consequences of aortic cross-clamping and unclamping. Anesthesiology 1979;50:462–6.
2. Grindlinger GA, Vegas AM, Manny J, Bush HL, Mannick JA, Hechtman HB. Volume loading and vasodilators in abdominal aortic aneurysmectomy. Am J Surg 1980;138:480–6.
3. Gelman S, McDowell H, Varner PD, et al. The reason for cardiac output reduction after aortic cross-clamping. Am J Surg 1988;155:578–86.
4. Gamulin Z, Forster A, Morel D, Simonet F, Aymon E, Favre H. Effects of infrarenal aortic cross-clamping on renal hemodynamics in humans. Anesthesiology 1984;61:394–9.
5. Gamulin Z, Forster A, Simonet F, Aymon E, Favre H. Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. Anesthesiology 1986;65:688–92.
6. Diehl JT, Cali RF, Hertzer NR, Beven EG. Complications of abdominal aortic reconstruction. An analysis of perioperative risk factors in 557 patients. Ann Surg 1983;197:49–56.
7. McCombs PR, Roberts B. Acute renal failure following resection of abdominal aortic aneurysm. Surg Gynecol Obstet 1979;148:175–8.
8. Ichikawa I, Pfeffer JM, Pfeffer MA, Hostetter TH, Brenner BM. Role of the angiotensin II in the altered renal function of congestive heart failure. Circ Res 1984;55:669–75.
9. Colson P, Ribstein J, Mimran A, Grolleau D, Chaptal PA, Roquefeuil B. Effect of angiotensin converting enzyme inhibition on blood pressure and renal function during open heart surgery. Anesthesiology 1990;72:23–7.
10. Gal TJ, Cooperman LH, Berkowitz HD. Plasma renin activity in patients undergoing surgery of the abdominal aorta. Ann Surg 1973;179:65–9.
11. Berkowitz HD, Shetty S. Renin release and renal cortical ischemia following aortic cross clamping. Arch Surg 1974;109: 612–7.
12. Loutzenhiser RD, Epstein M. Renal hemodynamic effects of calcium antagonists. Am J Med 1987;82:23–8.
13. Navar LG, Champion WGJ, Thomas CE. Effects of calcium channel blockade on renal vascular resistance responses to changes in perfusion pressure and angiotensin-converting enzyme inhibition in dogs. Circ Res 1986;58:874–81.
14. Humes HD. Role of calcium in pathogenesis of acute renal failure. Am J Physiol 1986;250:F579–89.
15. Schrier RW, Arnold PE, Van Putten VJ, Burke TJ. Cellular calcium in ischemic acute renal failure: role of the calcium entry blockers. Kidney Int 1987;32:313–21.
16. Wagner K, Albrecht S, Neumayer HH. Prevention of post-transplant acute tubular necrosis by the calcium antagonist diltiazem: a prospective randomized study. Am J Nephrol 1987;7:287–91.
17. Mimran A, Deschodt G. The role of the renin-angiotensin system in the renal and hormonal responses to tilt in normal man. Renal Physiol 1983;6:36–42.
18. McConachie I, Healy TEJ. ACE inhibitors and anaesthesia. Postgrad Med J 1989;65:273–4.
19. Colson P, Grolleau D, Chaptal PA, Ribstein J, Mimran A, Roquefeuil B. Effect of preoperative renin-angiotensin system blockade on hypertension following coronary surgery. Chest 1988;93:1156–8.
20. Kataja JHK, Kaukinen S, Viinamaki OVK, Metsa-Ketela TJA, Vapaatalo H. Hemodynamic and hormonal changes in patients pretreated with captopril for surgery of abdominal aorta. J Cardiovasc Anesth 1989;3:425–32.
21. Waeber B, Nussberger J, Juillerat L, Brunner H. Angiotensin converting enzyme inhibition: discrepancy between antihypertensive effect and plasma converting angiotensin inhibition. J Cardiovasc Pharmacol 1989;14(Suppl. 4):S57–S63.
22. Mimran A, Ribstein J. Effect of captopril on blood pressure and renal responses to acute saline loading in normal and essential hypertensive subjects. Clin Sci 1982;63:223s–5s.
23. Colson P, Capdevilla X, Cuchet D, et al. Does choice of the anesthetic influence renal function during infrarenal aortic surgery? Anesth Analg 1992;74:481–5.
24. Johnston WE, Balestrieri FJ, Plonk G, D'Souza V, Howard G. The influence of periaortic collateral vessels on the intraoperative hemodynamic effects of acute aortic occlusion in patients with aorto-occlusive disease or abdominal aortic aneurysm. Anesthesiology 1987;66:386–9.
25. Paul MD, Mazer CD, Byrick RJ, Rose DK, Goldstein MB. Influence of mannitol and dopamine on renal function during elective infrarenal aortic clamping in man. Am J Nephrol 1986;6:427–34.
26. Stein M, James PM, Kelly J, Brown D, Shircliffe AC. Renal protection during aortic cross-clamping. Ann Surg 1972;38: 681–9.
27. Elliott HL, Pasadini F, Reid JL. Effects of nicardipine on aldosterone and pressor mechanisms. Br J Clin Pharmacol 1985;20:995–1025.
28. Johnson PC. The myogenic response. News Physiol Sci 1991; 6:41–2.
29. Cohen AJ, Fray JC. Calcium ion dependence of myogenic renal plasma flow autoregulation: evidence from the isolated perfused rat kidney. J Physiol (Lond) 1982;330:449–60.
30. Lontzenhiser R, Epstein M, Hayashi K, Horton C. Direct visualization of the effects of endothelin on the renal microvasculature. Am J Physiol 1990;258:F61–8.
31. Firth JD, Ratcliffe PJ, Raine AE, Ledingham JGG. Endothelin: an important factor in acute renal failure? Lancet 1988;2:1179–82.
32. Eskinder H, Rusch NJ, Supan FD, Kampine JP, Bosnjak ZJ. The effects of volatile anesthetics on L- and T-type calcium channel currents in canine cardiac Purkinje cells. Anesthesiology 1991;74:919–26.

Influence of Hydroxyethyl Starch on Coagulation in Patients During the Perioperative Period

Yves Claes, MD, Jan Van Hemelrijck, MD, Mark Van Gerven, MD, Jozef Arnout, PhD, Jos Vermylen, MD, PhD, Burchard Weidler, MD, PhD, and Hugo Van Aken, MD, PhD

Department of Anesthesiology and Center for Thrombosis and Vascular Research, University Hospitals of the Katholieke Universiteit, Leuven, Belgium

The perioperative use of hydroxyethyl starch (HES) has been implicated as a possible cause of intracranial bleeding. The purpose of this study was to compare the influence on blood coagulation of the isovolemic replacement of 1-L blood loss with either 6% HES (molecular weight [MW] average: 450,000) or 5% human albumin during neurosurgery or lower abdominal surgery. Twenty patients scheduled for brain tumor surgery and 20 patients undergoing transabdominal hysterectomy were studied. The activated partial thromboplastin time, prothrombin time, fibrinogen concentration, factor VIII coagulant, von Willebrand factor antigen, platelet count, and the activated clotting time were compared after induction of anesthesia, after administration of 500 and 1000 mL of colloid solution, and 24 and 48 h postoperatively. All measured coagulation variables remained within physiologic range. Changes in coagulation indices were identical in neurosurgical and hysterectomy patients, except for a larger increase in fibrinogen concentration 24 and 48 h after hysterectomy. The acute phase reaction of factor VIII coagulant and von Willebrand factor, which plays a role in postoperative hypercoagulability, was attenuated by the use of HES. We conclude that isovolemic replacement of 1-L blood loss with either 6% HES (MW average: 450,000) or 5% human albumin does not interfere with normal hemostasis during and after neurosurgery or lower abdominal surgery.

(Anesth Analg 1992;75:24–30)

Hydroxyethyl starch (HES), a complex polysaccharide (molecular weight [MW] average: 450,000), is available in 6% aqueous solution for use as a plasma substitute. Desirable characteristics of HES are its oncotic properties (1), the long duration of its hemodynamic effects due to its long half-life (2–7), the absence of any risk of transmitting infectious diseases, the low incidence of anaphylactoid reactions (8,9), and the low cost compared with human albumin (10,11); however, the effect of HES on hemostasis is still controversial. Although the effect on hemostasis appears to be minimal when HES is used in recommended amounts (25 mL/kg body wt) (9,12), several authors have demonstrated an important influence on the factor VIII complex, resulting in a von Willebrand-like syndrome (13–15).

Several cases of intracranial coagulopathies associated with the use of HES have been reported in neurosurgical patients when HES was used for perioperative intravascular volume replacement during aneurysm surgery (16,17) or to treat vasospasm by hypervolemic hemodilution (15,18). The common factor in these case reports was the use of large amounts of HES (>1000 mL) or administration during several days. All the patients developed a von Willebrand-like and a hemophilia-like syndrome, characterized by a marked decrease in factor VIII coagulant (VIII:C) activity and von Willebrand factor antigen (vWF:Ag); the activated partial thromboplastin time (aPTT) was markedly prolonged. Using thromboelastography, Siegel et al. (19) have demonstrated the effects of HES (and dextran) on coagulation in vitro: both fibrin formation and clot strength were impaired. Stump et al. (14) demonstrated the effect of HES on factor VIII and aPTT by administering 1000 mL of a 6% HES solution to healthy volunteers after removal of 500 mL of blood; the reported decrease in factor VIII and the prolongation of the aPTT were greater than would be expected if they were simply the result of hemodilution. It may be that patients undergoing brain surgery are especially vulnerable to coagulation disorders, possibly as a result of defibrination after brain tissue destruction (20). Any drug with an effect on fibrin clot formation may aggravate the problem.

The purpose of the present study was to evaluate

Accepted for publication February 20, 1992.

Address correspondence to Dr. Van Aken, Department of Anesthesiology, University Hospitals of the Katholieke Universiteit Leuven, Herestraat 49, B-3000 Leuven, Belgium.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

the influence of 1000 mL of HES (MW average: 450,000) on per- and postoperative coagulation and to determine whether this influence is different in patients undergoing intracranial and intraabdominal procedures. One-thousand milliliters of HES is the amount of the colloid that is often used clinically during the perioperative period. This dose is below the recommended upper limit dose of 25 mL/kg, which has been shown not to cause any clinically significant alteration in coagulation.

Methods

The study was approved by the Ethical Committee for Research in Patients of the Katholieke Universiteit Leuven, and written, informed consent was obtained for all patients. Twenty patients scheduled for brain tumor surgery and 20 patients scheduled for transabdominal hysterectomy were studied. The expected blood loss for each surgical procedure was between 500 and 1000 mL. All patients were ASA physical status classification I or II, were between 18 and 65 yr of age, and had a body weight between 60 and 75 kg. Exclusion criteria were preexisting coagulopathies; abnormal preoperative coagulation screening tests (prothrombin time [PT], aPTT, platelet count); intake of drugs affecting hemostasis within 2 wk preoperatively (coumarin, heparin, acetylsalicylic acid, estrogens); as well as liver (bilirubin > 1 mg/dL, alkaline phosphatase > 135 U/L) or kidney (serum creatinine > 1.4 mg/dL) dysfunction (21).

Within each group, patients were randomly assigned to receive 1000 mL of fluid for volume replacement, either as a 6% HES (Plasmasteril, Fresenius, Germany) or a 5% human albumin solution in 0.9% NaCl. Intravascular volume replacement was performed isovolumetrically, and right atrium pressures were continuously measured. If necessary, a hematocrit of 35% was restored during the first 12 h after surgery by administration of erythrocyte concentrates.

The anesthetic technique included thiopental, fentanyl, pancuronium, and isoflurane in all patients. The lungs of all patients were mechanically ventilated with a 60% nitrous oxide in oxygen mixture.

In each patient, venous blood samples were obtained from a nonheparinized central venous catheter. Sampling times were immediately after induction of anesthesia (sample 1), after administration of 500 mL (sample 2) and 1000 mL (sample 3) of the colloid solution, and 24 (sample 4) and 48 h (sample 5) postoperatively. The following coagulation tests were performed on a citrated blood sample at each sampling time: aPTT, PT, thrombin time, fibrinogen, factor VIII:C, and the vWF:Ag. Factor VIII:C was measured in a one-stage assay adapted to an automated coagulometer ACL-810 (IL, Milan, Italy) using severe hemophilia A plasma and a micronized silica aPTT reagent (IL, Milan, Italy). Pooled plasma, obtained from 20 healthy donors and calibrated against the second international standard for factor VIII and vWF activities in plasma, was used as a reference in all assays. The vWF:Ag was measured with an enzyme-linked immunosorbent assay (ELISA) based on two murine monoclonal antibodies raised against human vWF (22). Platelet count was performed on an anticoagulated blood sample (EDTA). An activated clotting time was measured with the Hemochron 400 (International Technodyne Corporation, Metuchen, N.J.) on a fresh blood sample.

Data are reported as mean values and standard deviation (SD). One-way analysis of variance with Bonferroni's correction and Tukey's test for multiple comparisons were used for statistical analysis, and $P < 0.05$ was considered significant.

Table 1. Demographic Variables of 20 Neurosurgery and 20 Hysterectomy Patients

Study group	Age (yr) (mean value ± SD)	Gender distribution (female/male)
Hysterectomy		
HES	47 ± 9	10/0
HA	47 ± 10	10/0
Neurosurgery		
HES	49 ± 15	6/3
HA	49 ± 15	8/3

HES, 6% hydroxyethyl starch; HA, 5% human albumin.

Results

Although the four treatment groups were identical with regard to age and weight, the hysterectomy groups obviously included female patients only, unlike the neurosurgery groups (Table 1).

The results of the coagulation tests are summarized in Tables 2–9. The aPTT did not change significantly during the study period (Table 2). Although a significant decrease in PT, expressed as percent of normal ($P < 0.001$), was observed after administration of 1 L of colloid solution, as well as 24 h postoperatively, the PT returned to normal within 48 h, and the changes were identical in all treatment groups (Table 3).

In all patients, a significant increase in fibrinogen concentration ($P < 0.001$) was observed 24 and 48 h postoperatively (Table 4). The increase in fibrinogen concentration was more pronounced in gynecologic than in neurosurgical patients; however, no difference could be observed between patients receiving HES and human albumin in each surgery group. A

Table 2. Activated Partial Thromboplastin Time (s)

Sample time	Hysterectomy group HES (n = 10)	Hysterectomy group HA (n = 10)	Neurosurgical group HES (n = 11)	Neurosurgical group HA (n = 9)
After induction	31.2 ± 2.7	31.5 ± 2.1	31.2 ± 4.8	29.7 ± 5.2
0.5 L of colloid	31.7 ± 6.2	31.5 ± 2.9	31.7 ± 3.9	29.6 ± 4.9
1 L of colloid	32.8 ± 7	31.1 ± 3.6	32.4 ± 5.6	29.5 ± 4.9
24 h postoperatively	32.6 ± 4.5	29.7 ± 4.7	32.6 ± 3.5	28.3 ± 3
48 h postoperatively	33.8 ± 5.5	30.3 ± 5	30.1 ± 2.3	27.4 ± 2.1

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are expressed as mean values ± SD.

Table 3. Prothrombin Time (%)

Sample time	Hysterectomy group HES (n = 10)	Hysterectomy group HA (n = 10)	Neurosurgical group HES (n = 11)	Neurosurgical group HA (n = 9)
After induction	86.3 ± 16.7	81.6 ± 15.1	84.9 ± 17.2	82.7 ± 19.6
0.5 L of colloid	77.4 ± 14.7[a]	73.5 ± 14.7[a]	78.7 ± 17.1[a]	73.6 ± 16[a]
1 L of colloid	64.5 ± 15.8[a]	67.8 ± 15.8[a]	75.8 ± 18.4[a]	69.1 ± 18.1[a]
24 h postoperatively	61.5 ± 16[a]	66.1 ± 16.3[a]	70.9 ± 19.6[a]	67.2 ± 14.7[a]
48 h postoperatively	74.6 ± 27	79.4 ± 17.8	78.7 ± 17.8	88.2 ± 14.6

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.
[a]Change over time, $P < 0.001$; no significant differences between groups.

Table 4. Fibrinogen (g/L)

Sample time	Hysterectomy group HES (n = 10)	Hysterectomy group HA (n = 10)	Neurosurgical group HES (n = 11)	Neurosurgical group HA (n = 9)
After induction	2.20 ± 0.47	2.58 ± 0.60	2.65 ± 0.79	1.98 ± 1.07
0.5 L of colloid	2.01 ± 0.39	2.33 ± 0.58	2.40 ± 0.67	1.75 ± 0.80
1 L of colloid	1.97 ± 0.46	2.03 ± 0.64	2.58 ± 0.71	1.72 ± 0.87
24 h postoperatively	3.37 ± 0.81[a]	3.71 ± 1.25[a]	3.17 ± 0.55[a]	2.33 ± 0.66[a]
48 h postoperatively	4.60 ± 1.25[a]	5.63 ± 1.16[a]	4.24 ± 0.99[a]	3.07 ± 1.17[a]

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.
[a]Change over time, $P < 0.001$; difference between groups, $P < 0.01$.

shortening of the thrombin time was observed at sample times 3, 4, and 5 in patients receiving HES (Table 5).

Factors VIII:C and vWF:Ag were significantly increased ($P < 0.001$) 24 and 48 h after surgery in the groups receiving human albumin (Tables 6 and 7). In contrast, no significant changes in factor VIII:C and vWF:Ag were observed for all measurement times when HES was administered. Table 8 shows the individual values of factor VIII:C after the administration of 1 L of colloid. Factor VIII:C was <40% in one gynecologic patient (Table 8).

Although a significant decrease in platelet count was observed at the end of the operation (sample 3), the variability among patients was high, and there was no difference between treatment groups (Table 9).

The activated clotting time values were similar for all measurement times and treatment groups; however, they were characterized by a large interpatient variability (Table 10). None of the patients lost an abnormally large quantity of blood or experienced a clinically perceptible coagulation disorder.

Discussion

We were unable to demonstrate any difference in the changes in coagulation between neurosurgical and gynecologic patients receiving 1 L of a 6% HES (MW average: 450,000) solution for isovolemic intravascu-

Table 5. Thrombin Time (s)

Sample time	Hysterectomy group HES ($n = 10$)	Hysterectomy group HA ($n = 10$)	Neurosurgical group HES ($n = 11$)	Neurosurgical group HA ($n = 9$)
After induction	21.1 ± 2.4	21.6 ± 1.84	22.0 ± 2.1	23.8 ± 2.4
0.5 L of colloid	21.9 ± 1.5	20.8 ± 2.0	18.2 ± 1.9	23.0 ± 2.6
1 L of colloid	14.9 ± 1.7[a,b]	20.4 ± 2.3[b]	16.0 ± 1.9[a,b]	21.1 ± 2.5[b]
24 h postoperatively	16.8 ± 2.0[a,b]	19.7 ± 3.4[b]	16.8 ± 2.1[a,b]	18.5 ± 2.7[b]
48 h postoperatively	17.5 ± 2.0[a,b]	20.1 ± 2.4[b]	17.2 ± 1.7[a,b]	19.4 ± 2.3[b]

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.
[a]Change over time, $P < 0.001$.
[b]Differences between groups, $P < C.01$.

Table 6. Factor VIII Coagulant Activity (%)

Sample time	Hysterectomy group HES ($n = 10$)	Hysterectomy group HA ($n = 10$)	Neurosurgical group HES ($n = 11$)	Neurosurgical group HA ($n = 9$)
After induction	129 ± 56	100 ± 57	93 ± 36	226 ± 109
0.5 L of colloid	148 ± 58	117 ± 100	106 ± 52	228 ± 82
1 L of colloid	113 ± 50	144 ± 139	87 ± 29	216 ± 83
24 h postoperatively	109 ± 66[a]	226 ± 140[a,b]	97 ± 41[a]	383 ± 141[a,b]
48 h postoperatively	147 ± 89[a]	224 ± 106[a,b]	136 ± 60[a]	428 ± 147[a,b]

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.
[a]Difference between groups, $P < 0.001$.
[b]Change over time, $P < 0.001$.

Table 7. von Willebrand Factor Antigen (%)

Sample time	Hysterectomy group HES ($n = 10$)	Hysterectomy group HA ($n = 10$)	Neurosurgical group HES ($n = 11$)	Neurosurgical group HA ($n = 9$)
After induction	144 ± 47	112 ± 53	125 ± 41	144 ± 66
0.5 L of colloid	201 ± 249	111 ± 51	111 ± 52	118 ± 24
1 L of colloid	122 ± 53	106 ± 53	104 ± 33	118 ± 36
24 h postoperatively	130 ± 57[a]	187 ± 50[a,b]	100 ± 51[a]	170 ± 40[a,b]
48 h postoperatively	147 ± 78[a]	256 ± 32[a,b]	130 ± 64[a]	212 ± 67[a,b]

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.
[a]Change over time, $P < 0.001$.
[b]Difference between groups, $P < 0.01$.

lar volume replacement. Moreover, all the changes in coagulation that could be observed in patients treated with 1 L of a 6% HES or a 5% human albumin solution were within physiologic limits and did not interfere with normal hemostasis. Therefore, 1 L of a 6% HES or a 5% human albumin solution appears to be devoid of any negative influence on coagulation in surgical patients; however, these conclusions may not be valid if larger amounts of colloids are administered. There may also be a difference between neurosurgical patients and patients undergoing other types of surgery in these circumstances.

Although the gender distribution of both surgery groups was obviously different, patients treated with estrogens were excluded. No major differences have been reported between coagulation in male and female patients. Moreover, the gender distribution of patients receiving HES or human albumin was identical.

An important observation appears to be the effect of HES on the factor VIII complex. Bleeding in a neurosurgical patient is obviously disastrous. Therefore, it is important that coagulant levels do not decrease below dangerous limits. In treating patients

Table 8. Individual Values of Factor VIII Coagulant Activity (%) After Administration of 1 L of Colloid

Patient No.	Hysterectomy group		Neurosurgery group	
	HES	HA	HES	HA
1	78	100	77	111
2	62	58	98	234
3	79	110	183	97
4	55	169	111	71
5	38	67	86	92
6	143	200	125	118
7	63	105	99	77
8	218	241	54	106
9	158	67	97	60
10	79	91	73	
11			79	

HES, 6% hydroxyethyl starch; HA, 5% human albumin.

with hemophilia A undergoing neurosurgery, most hematologists would maintain factor VIII:C activity >40%–50%. Although no difference was observed between the groups, factor VIII:C decreased to 38% of the preoperative level after the administration of 1 L of HES in one patient undergoing hysterectomy. The lowest level of factor VIII:C observed in the neurosurgical patients was 54%. The probability that a clinically important (factor VIII:C < 50%) difference in factor VIII:C between HES- and human albumin-treated neurosurgical patients would have been detected by the test procedure is 92%, because the calculated β-error for the observed factor VIII:C value of 87% ± 29% after 1 L of HES and for the number of patients studied is 0.084. Factor VIII activity levels <50% will certainly be observed when larger patient populations are studied; however, the present observations suggest that this will be equally frequent after 1 L of 6% HES or 5% human albumin.

Although a marked increase in factor VIII:C activity and vWF:Ag was observed postoperatively in patients treated with 1 L of 5% human albumin (control group), these coagulation parameters remained unchanged compared with the preoperative values in patients receiving 1 L of a 6% HES solution. An increase in factor VIII activity plays a major role in postoperative hypercoagulability (12,23). We speculate that the peroperative administration of 1 L of HES may exert a protective influence against postoperative thromboembolism by inhibiting the postoperative increase in factor VIII activity and by the rheologic effect of hemodilution. This speculation is supported by the observations of Heilmann et al. (24), who found a lower incidence of deep venous thrombosis after cesarean section in patients who received 1500 mL of HES compared with patients treated with low-dose heparin. The effect of HES on the factor VIII complex is similar to the effect of dextran (25); however, the antihemostatic effect of dextran appears to be more pronounced. Although HES and dextran are both complex polysaccharides, their molecular structures are different, and it has not yet been demonstrated that their effects on coagulation on the molecular scale are identical.

When compared to baseline, a significant decrease in PT values, expressed in percent, was observed after administration of 1000 mL of colloid, and 24 h after operation. This observation was probably the result of dilution of the coagulation factors by approximately 25%. The PT returned to baseline values within 48 h.

A significant increase in fibrinogen concentration was observed in all groups 24 and 48 h after surgery. This has been previously reported (23,26) as being the result of the acute phase reaction. Of note, the increase in fibrinogen appears to be more pronounced in patients undergoing hysterectomy than in neurosurgical patients, probably due to a more extensive surgical trauma. This may contribute to the high incidence of postoperative thromboembolic accidents after lower abdominal surgery.

The significant shortening of the thrombin times after infusion of 1 L of HES, reflecting an accelerated conversion of fibrinogen to fibrin, may indicate the influence of HES on the polymerization of fibrin monomers. This observation is comparable to the

Table 9. Platelet Count (platelets × 10^9/L)

Sample time	Hysterectomy group		Neurosurgical group	
	HES (n = 10)	HA (n = 10)	HES (n = 11)	HA (n = 9)
After induction	242 ± 63	260 ± 65	263 ± 119	241 ± 73
0.5 L of colloid	263 ± 50	233 ± 68	264 ± 94	231 ± 75
1 L of colloid	231 ± 46	205 ± 77	264 ± 85	217 ± 65
24 h postoperatively	250 ± 89	234 ± 90	276 ± 87	236 ± 79
48 h postoperatively	217 ± 58	239 ± 70	246 ± 70	212 ± 89

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.

Table 10. Activated Clotting Time (s)

Sample time	Hysterectomy group		Neurosurgical group	
	HES (n = 10)	HA (n = 10)	HES (n = 11)	HA (n = 9)
After induction	143 ± 23	123 ± 34	136 ± 27	157 ± 30
0.5 L of colloid	116 ± 37	123 ± 13	145 ± 34	152 ± 32
1 L of colloid	112 ± 38	128 ± 27	142 ± 35	150 ± 27
24 h postoperatively	107 ± 34	135 ± 33	151 ± 33	152 ± 28
48 h postoperatively	150 ± 41	123 ± 41	149 ± 27	139 ± 30

HES, 6% hydroxyethyl starch; HA, 5% human albumin.
Data are presented as mean values ± SD.

results of other investigations (27,28) on the in vitro and in vivo effects of HES on the coagulation system. This influence may result in friable clots that microscopically lack a tight meshwork (29,30).

Because of the high variability and low number of patients, this study was not likely to detect a difference in platelet count between the groups. The power of the study with respect to the platelet count was only ±0.4; however, to evaluate the statistical power, it is necessary to consider the clinical importance of the numerical values. To conclude that the effect of the treatment on the platelet count would have been different, the minimal difference between the groups should have been on the order of 80×10^9 platelets/L, considering the number of patients and the variability observed in this study. Therefore, we cannot exclude from the data of this investigation the fact that the two treatments may have had different effects on the platelet count. However, with regard to the other measurements, the variability among patients, compared with the magnitude of clinically important differences, was small enough to conclude that the chance of not recognizing a clinically important difference between the treatment groups was low, because the power of the test for each of these measurements was sufficiently high to exclude a type II error with a probability of ±90%.

In conclusion, the isovolemic volume replacement of blood loss with 1 L of a 6% HES (MW average: 450,000) solution or 1 L of a 5% human albumin solution appears not to interfere with normal hemostasis during and after surgery. Coagulation is identical in neurosurgical patients receiving HES or human albumin. The peroperative administration of 1 L of a 6% HES solution prevents the postoperative increase in factor VIII:C activity, a factor contributing to postoperative hypercoagulability states.

References

1. Haupt M, Rackow E. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin and saline solutions. Crit Care Med 1982;10:159–62.
2. Kraatz J, van Ackern K, Glocke H, Martin E, Peter K, Shmitz E. Circulatory changes during preoperative isovolemic hemodilution with a mixed solution of HES and 5% human albumin. Anaesthesist 1975;24:210–5.
3. Hempel V, Metzger G, Unseld H, Schorer R. The influence of hydroxyethyl starch solutions on circulation and on kidney function in hypovolemic patients. Anaesthesist 1975;24:198–201.
4. Lazrove S, Waxman K, Shippy C, Shoemaker W. Hemodynamic blood volume and oxygen transport responses to albumin and hydroxyethylstarch infusions in critically ill postoperative patients. Crit Care Med 1980;8:302–6.
5. Puri V, Paidipaty B, White L. Hydroxyethylstarch for resuscitation of patients with hypovolemia and shock. Crit Care Med 1981;9:833–7.
6. Rackow E, Falk JL, Fein A, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983;11:839–50.
7. Moggio R, Chan Rha C, Somberg E, Praeger P, Pooley R, Reed G. Hemodynamic comparison of albumin and hydroxyethylstarch in postoperative cardiac surgery patients. Crit Care Med 1983;11:943–5.
8. Beez M, Dietl H. Retrospektive Betrachtung der Häufigkeit anaphylaktoider Reaktion nach Plasmasteril® und Longasteril®. Infusionsther Klin Ernahr 1979;6:23–6.
9. Harke H, Pieper CH, Meredig J, Rüssler P. Rheologische und gerinnungsphysiologische untersuchungen nach Infusion von HÄS 200/0.5 und Dextran 40. Anesthesist 1980;29:71–6.
10. Donnelly A. Albumin/hetastarch drug reutilization review in an operating room pharmacy. Drug Intell Clin Pharm 1987;2:286–9.
11. Yanwong Y, Abromowitz P, Mansur J. Changing use patterns of plasma volume expanders through educational intervention. Am J Hosp Pharm 1987;44:102–5.
12. Strauss R. Review of the effects of hydroxyethylstarch on the blood coagulation system. Transfusion 1981;21:299–302.
13. Strauss R, Stump D, Henrikses R. Hydroxyethylstarch accentuates von Willebrand's disease. Transfusion 1985;25:235–7.
14. Stump D, Strauss R, Henriksen R, Petersen R, Saunders R. Effects of hydroxyethylstarch on blood coagulation, particularly factor VIII. Transfusion 1985;25:349–54.
15. Sanfelippo M, Suberviola P, Geimer N. Development of a von Willebrand-like syndrome after prolonged use of hydroxyethylstarch. Am J Clin Pathol 1987;88:653–5.
16. Symington B. Hetastarch and bleeding complications. Ann Intern Med 1986;105:627–8.
17. Cully M, Larson C, Silverberg G. Hetastarch coagulopathy in a neurosurgical patient. Anesthesiology 1987;66:706–7.
18. Damon L, Adams M, Stricker R, Ries C. Intracranial bleeding during treatment with hydroxyethylstarch. N Engl J Med 1987;317:964–5.
19. Siegel M, Bjoraker D, Gravenstein N, Goodwin S. Changes in clot formation induced by hydroxyethylstarch and dextran 40:

assessment by thromboelastograph and sonoclot (abstract). Anesthesiology 1988;89:A13.
20. Goodnight S, Kenoyer G, Rapaport S. Defibrination after brain tissue destruction: a serious complication of head injury. N Engl J Med 1974;290:1043.
21. Dienes H, Gerharz CD, Wagner R, Weber M, John HD. Accumulation of hydroxyethylstarch in the liver of patients with renal failure and portal hypertension. J Hepatol 1986;3: 223–7.
22. Tornai I, Declerck PJ, Smets L, et al. Measurement of von Willebrand factor antigen in plasma and platelets with an enzyme-linked immunosorbent assay based on two murine monoclonal antibodies. Haemostasis 1991;21:125–34.
23. Colman RW. Hemostasis and thrombosis: basic principles and clinical practice. 2nd ed. Philadelphia: Lippincott, 1987.
24. Heilmann L, Heitz R, Koch F-U, Ose Ch. Die perioperative Thromboseprophylaxe beim Kaiserschnitt: Ergebnisse einer randomisierten prospektiven Vergleichsuntersuchung mit 6% Hydroxyäthylstärke 0.62 und Low-dose-Heparin. Z Geburtshilfe Perinatol 1991;195:11–5.
25. Aberg M, Heduer U, Bergentz SE. Effect of dextran on factor VIII (antihemophilic factor) and platelet function. Ann Surg 1979;189:243–7.
26. Butler M. Thromboelastography during and after elective abdominal surgery. Thromb Haemost 1978;39:488–95.
27. Matsuda T, Murakami M. Effects of hydroxyethylstarch on blood coagulation and fibrinolysis. I. In vitro studies. Jpn J Clin Hematol 1972;13:831–6.
28. Matsuda T, Murakami M. Effects of hydroxyethylstarch on blood coagulation and fibrinolysis. II. In vivo studies. Jpn J Clin Hematol 1972;13:934–41.
29. Carr ME. Effect of hydroxyethylstarch on the structure of thrombin and reptilase-induced fibrin gels. J Lab Clin Med 1986;108:556–61.
30. Strauss RG, Stump DC, Henriksen RA, Saunders R. Effect of hydroxyethylstarch on fibrinogen, fibrin clot formation and fibrinolysis. Transfusion 1985;25:230–4.

Effects of Fentanyl on α-Aminoisobutyric Acid Transfer Across the Blood-Brain Barrier

Oak Za Chi, MD, Hwu Meei Wei, PhD, Mujahid Anwar, MD, Arabinda K. Sinha, PhD, Sanford L. Klein, DDS, MD, and Harvey R. Weiss, PhD

Departments of Anesthesia, Pediatrics, and Physiology and Biophysics, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey

The effect of fentanyl on the transfer of small hydrophilic molecules across the blood-brain barrier was studied in rats by measuring the blood-brain transfer coefficient (K_i) and the regional cerebral blood flow (rCBF) and by calculating the capillary permeability-surface area product. In the control group (n = 14), after a femoral artery and vein were catheterized under isoflurane anesthesia, the rats were allowed to remain awake for 1.5 h before measuring K_i (n = 8) using intravenous ^{14}C-α-aminoisobutyric acid or rCBF (n = 6) using ^{14}C-iodoantipyrine. In the fentanyl groups, rats were injected with 25 μg/kg (low dose) (n = 6) or 100 μg/kg (high dose) of fentanyl (n = 14), followed by a continuous infusion at a rate of 50 or 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively. Their lungs were mechanically ventilated. The K_i (low dose, n = 6; high dose, n = 8) and rCBF (high dose, n = 6) were measured 1 h after fentanyl infusion. The K_i was lower in 9 of 13 brain regions in the low-dose fentanyl group and in 7 of 13 brain regions in the high-dose fentanyl group than in the control animals. The average value of K_i in all the brain regions was 8.6 ± 4.6 $\mu L \cdot g^{-1} \cdot min^{-1}$ in the control group, 5.2 ± 2.9 $\mu L \cdot g^{-1} \cdot min^{-1}$ in the low-dose fentanyl group, and 5.7 ± 2.9 $\mu L \cdot g^{-1} \cdot min^{-1}$ in the high-dose fentanyl group. High-dose fentanyl did not significantly affect rCBF in any brain region studied. The value of the regional permeability-surface area product was similar to the corresponding regional K_i in the groups studied. In conclusion, fentanyl decreased the transfer of small hydrophilic molecules across the blood-brain barrier, as demonstrated by a decreased K_i and permeability-surface area product, without significant changes in rCBF.

(Anesth Analg 1992;75:31–6)

The blood-brain barrier (BBB) is an anatomic and functional structure that plays an important role in maintaining the homeostasis of the brain. An intact BBB is required to protect the brain against various circulating molecules and neurotoxins in the plasma (1,2). The characteristic property of the BBB may be changed with osmotic agents (3), sudden hypertension, extreme hypotension with the use of vasodilating agents (4,5), trauma, inflammation, anoxia, and seizures (6).

Recently, Saija et al. (7) demonstrated that both pentobarbital and ketamine decreased the transfer of small hydrophilic molecules across the BBB even though ketamine increased cerebral glucose utilization. Our previous study (8) showed that the blood-brain transfer coefficient (K_i) for small hydrophilic molecules was decreased under isoflurane anesthesia. We hypothesized that the transfer of these substances across the BBB would also be decreased during fentanyl administration because both are anesthetic and lipophilic agents.

In our study, the effect of fentanyl on K_i was measured using ^{14}C-α-aminoisobutyric acid (^{14}C-AIB). α-Aminoisobutyric acid is a small, synthetic, inert neutral amino acid with a molecular mass of 104 daltons that does not cross the BBB rapidly (9). Once it does cross, however, it is quickly absorbed and concentrated in the brain cells. Its backflux into blood is minimized (10). Therefore, transfer across the BBB is the rate-determining factor in the accumulation of AIB in brain cells. Regional cerebral blood flow (rCBF) was determined using ^{14}C-iodoantipyrine. The extraction fraction and the capillary permeability-surface area product were calculated from rCBF and K_i.

This work was supported by grants from the American Heart Association, New Jersey Affiliate (89-021, 90-014) and the United States Public Health Service (NS25100).

Accepted for publication March 16, 1992.

Address correspondence to Dr. Chi, Department of Anesthesia, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, CN 19, One Robert Wood Johnson Place, New Brunswick, NJ 08903-0019.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Methods

This study was approved by our institutional animal care and use committee. Thirty-four adult male Long Evans rats weighing 300–400 g were divided into the following three groups: control (n = 14); low-dose fentanyl (25 μg/kg) (n = 6); and high-dose fentanyl (100 μg/kg) (n = 14). For the control group, we used awake, restrained animals for the measurement of rCBF and K_i, as described previously (7,11,12). Under 2% isoflurane anesthesia, a femoral artery catheter was placed to monitor heart rate and blood pressure and to collect blood samples for the analysis of blood gases and pH. A femoral vein was also catheterized to administer radioactive tracers. After catheterization, the area of incision was infiltrated with 0.25% bupivacaine. Isoflurane was then discontinued, and animals were restrained and remained awake for 1.5 h. In 8 of 14 control rats, rCBF was measured. Regional K_i was determined in the other six rats in the control group.

In the fentanyl groups, under 2% isoflurane anesthesia, a femoral artery and two femoral veins were catheterized and a tracheostomy performed. Femoral arterial and venous catheters were used for the same purpose as in the control group, except that an additional femoral venous catheter was needed in the fentanyl groups for the continuous infusion of fentanyl. Isoflurane was discontinued after catheterization and tracheostomy. When the end-tidal isoflurane concentration decreased to 0.5%, fentanyl (25 μg/kg [low dose] or 100 μg/kg [high dose]) was injected intravenously over a 5-min period. The injection was followed by a slow, continuous infusion at a rate of twice the initial dose per hour (50 and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively) up to the time of decapitation. Animals were given vecuronium (1 mg/kg IV) and were mechanically ventilated. One hour after fentanyl infusion, K_i was determined in 8 of 14 rats in the high-dose fentanyl group and in the 6 rats in the low-dose fentanyl group. The rCBF was measured in the other six rats in the high-dose fentanyl group. Body temperature of the animals was maintained at 37 ± 0.5°C with a servocontrolled heat lamp. Arterial blood pressure was continuously measured and recorded. A 0.2-mL arterial blood sample was withdrawn anaerobically and analyzed for Pao_2, $Paco_2$, and pH before the determination of rCBF and K_i. Fronto-occipital platinum needle electrodes were inserted in the scalp to monitor the electroencephalogram in three animals in the high-dose fentanyl group.

To measure rCBF, ^{14}C-iodoantipyrine (Amersham, Arlington Heights, Ill.) was infused into the venous catheter by means of an infusion pump (Sage Instruments, Cambridge, Mass.). At the time of entry of the isotope into the venous circulation, the arterial catheter was cut to a length of 15–20 mm to minimize smearing in the sampling catheter. Timed blood samples were withdrawn from the arterial catheter and collected approximately every 3 s in glass capillary tubes. These samples were collected over a period of approximately 60 s, at which time the rat was decapitated to terminate perfusion at the moment the last sample was obtained. For the fentanyl groups, fentanyl was continuously infused until the time of decapitation. The brain was removed and dissected in a humid chamber. The following regions were dissected and weighed: olfactory bulb, anterior cortex, lateral cortex, posterior cortex, hippocampus, cortical white, basal ganglia, hypothalamus, superior colliculus, inferior colliculus, cerebellum, pons, and the medulla. Blood and tissue samples were then placed in a tissue solubilizer (Soluene, Packard, Downers Grove, Ill.); 24 h later, a counting fluid (Dimiscint, National Diagnostic, Manville, NJ) was added, and they were agitated. These samples were counted with a Beckman LS-230 liquid scintillation counter. Quench curves were prepared with carbon tetrachloride and the isotope counts.

Regional blood flow was calculated with a computer program based on the following equation:

$$C_i(T) = \lambda K \int_0^T C_A e^{-K(T-t)}\, dt;$$

where $C_i(T)$ is the tissue concentration of ^{14}C-iodoantipyrine at the time of decapitation, λ the tissue:blood partition coefficient, C_A the arterial concentration of the tracer, and t time; K = mF/W, where m is the constant related to diffusion and F/W the blood flow per unit mass of tissue. The λ value of 0.8, as calculated by Sakurada et al. (13), was used.

To determine K_i, after the final determination of heart rate, blood pressure, and blood gases, 20 μCi of ^{14}C-AIB (Amersham) was rapidly injected intravenously and flushed with 0.5 mL of normal saline solution. Blood samples were collected from the arterial catheter at 15-s intervals for the first 2 min and then every minute for the next 8 min. Five minutes after the injection of ^{14}C-AIB, 10 μCi of ^{3}H-dextran (molecular weight 70,000) (Amersham) was injected intravenously and flushed with 0.5 mL of normal saline solution. After collecting the 10-min arterial blood sample, the animals were decapitated. For the fentanyl groups, fentanyl was continuously infused until time of decapitation. The same brain regions that were used for rCBF determination were dissected in a humid chamber, weighed, and placed in Soluene. Twenty-four hours later, a counting fluid (Dimiscint) was added. Arterial blood samples were centrifuged and the plasma separated. They were processed the same way as the brain samples were for scintillation counting. Plasma and brain samples

were counted on a liquid scintillation counter equipped for dual-label counting. Quench curves were prepared using carbon tetrachloride, and all samples were automatically corrected for quenching.

The blood-brain transfer coefficient for ^{14}C-AIB was determined assuming the unidirectional transfer of ^{14}C-AIB over the 10-min period of the experiment using the following equation, as described previously by Gross et al. (12):

$$K_i = \frac{A_m - (V_p \cdot CT)}{\int_0^T C_p(t)\,dt},$$

where A_m is the amount of ^{14}C-AIB radioactivity in the tissue per gram and V_p the volume of plasma retained in the tissue. This is determined from the results of the ^{3}H-dextran data and the equation $V_p = A_m'/C_p'$, where A_m' is the amount of ^{3}H-dextran radioactivity in the tissue per gram and C_p' the concentration of ^{3}H-dextran in the plasma at time of decapitation; $C_p(t)$ is the arterial concentration of ^{14}C-AIB over time t and CT the arterial plasma concentration of ^{14}C-AIB at time of decapitation. In the equation to determine K_i, $V_p \cdot CT$ is a correction term that accounts for the ^{14}C-AIB retained in the vascular compartment of the tissue A_m.

The extraction fraction (E) was calculated using the equation $E = K_i/FV_f$, where F is the blood flow and V_f the fraction of blood that contains ^{14}C-AIB. A tissue hematocrit of 30% was used, which is an average value of the multiple brain regions obtained previously from the study by Cremer et al. (14). A permeability-surface area (PS) product for ^{14}C-AIB was calculated with the formula $PS = -FV_f \ln(1 - E)$.

Analysis of variance and multiple comparisons with the Duncan's post hoc procedure were used to determine the differences among various brain regions and among the groups. Results are expressed as mean values ± SD unless otherwise specified. A value of $P < 0.05$ was considered significant.

Results

Hemodynamic and blood gas variables in the control and fentanyl groups are presented in Table 1. These variables were obtained after 1 h of fentanyl infusion and just before taking the measurements of rCBF and K_i and 1.5 h after recovery from surgery in the control group. Arterial blood pressure was not significantly different between the fentanyl groups, but heart rate was significantly lower in the fentanyl groups than in the control group. The pH of the low-dose fentanyl group was lower than that of the control group. The electroencephalogram in the high-dose fentanyl group was characterized by high-amplitude delta rhythm without seizure activity at the time of K_i or rCBF measurement.

Table 1. Hemodynamic and Blood Gas Variables in the Control and Fentanyl Groups

	Control group (n = 14)	Fentanyl groups	
		Low dose (n = 6)	High dose (n = 14)
Systolic blood pressure (mm Hg)	143 ± 18	160 ± 18	150 ± 14
Diastolic blood pressure (mm Hg)	113 ± 13	114 ± 18	114 ± 9
Mean blood pressure (mm Hg)	123 ± 13	129 ± 17	126 ± 10
Heart rate (beats/min)	475 ± 43	302 ± 44*	293 ± 44*
Pao_2 (mm Hg)	93 ± 11	108 ± 19	111 ± 25
$Paco_2$ (mm Hg)	33 ± 4	32 ± 3	34 ± 3
pH	7.41 ± 0.08	7.36 ± 0.02*	7.35 ± 0.05

Data are expressed as mean values ± SD.
*Significantly different from control value.

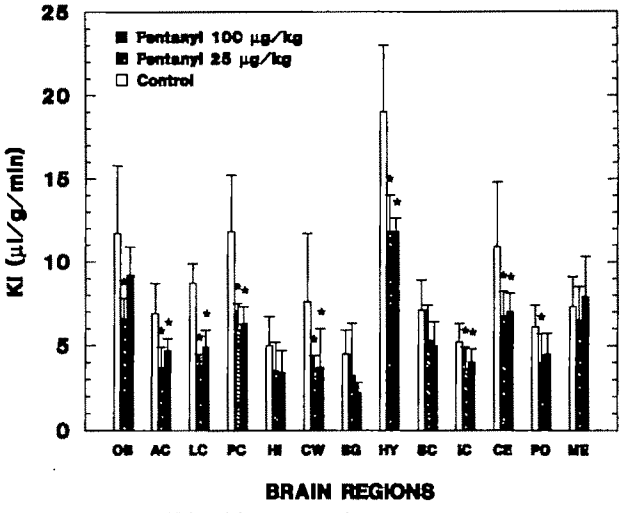


Figure 1. Regional blood-brain transfer coefficient (K_i) in examined regions of the control and the low- and high-dose fentanyl groups. Results are presented as mean values ± SD. OB, olfactory bulb; AC, anterior cortex; LC, lateral cortex; PC, posterior cortex; HI, hippocampus; CW, cortical white; BG, basal ganglia; HY, hypothalamus; SC, superior colliculus; IC, inferior colliculus; CE, cerebellum; PO, pons; ME, medulla. *Significantly different from the corresponding control value.

The mean K_i was 8.6 ± 4.6 $\mu L \cdot g^{-1} \cdot min^{-1}$ in the control group and 5.2 ± 2.9 and 5.7 ± 2.9 $\mu L \cdot g^{-1} \cdot min^{-1}$ in the low- and high-dose fentanyl groups, respectively. Experimentally determined values for regional K_i are shown in Figure 1. The K_i was significantly lower in 9 of 13 brain regions in the low-dose group and in 7 of 13 brain regions of the high-dose group compared with the control group. The K_i in the low-dose fentanyl group was not

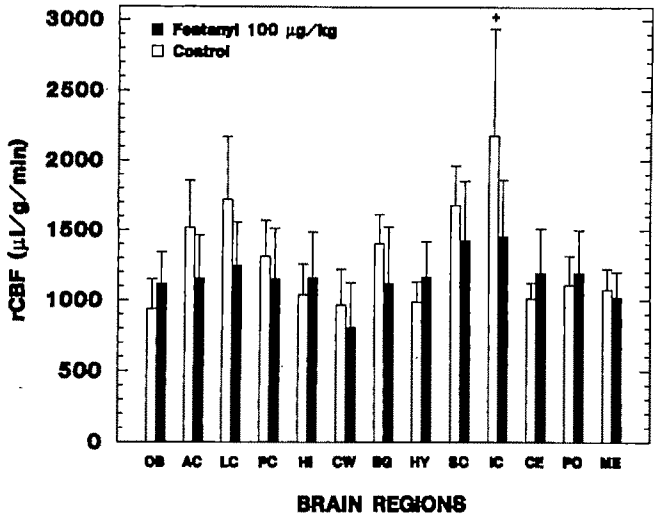


Figure 2. Regional cerebral blood flow (rCBF) in examined regions of the control and the high-dose fentanyl groups. Results are presented as mean values ± SD. There was no significant difference between the control group and the high-dose fentanyl group in each rCBF. +Significantly different from all other brain regions of the control group. Abbreviations as in Figure 1.

different from that in the high-dose fentanyl group in any brain region (Figure 1). Regional K_i of the hypothalamus was significantly higher than that of other brain regions studied in all three groups of animals. Transport of ^{14}C-AIB was not linearly related to the dose of fentanyl.

Results of rCBF are shown in Figure 2. There were no significant differences in rCBF between the control and the high-dose fentanyl groups. Within the control group, however, there were regional differences in rCBF. The inferior colliculus flow was higher than that of all other regions. Cortical white and olfactory bulb flow were lower than anterior and lateral cortex and basal ganglia flow. Fentanyl anesthesia decreased these regional differences. Only flows in the inferior and superior colliculus were higher than cortical white flow.

The extraction fraction and the regional permeability-surface area product in almost all the brain regions of the high-dose fentanyl group were lower than those of the control group (Figure 3). The average permeability-surface area product was approximately 34% lower in the high-dose fentanyl group than in the control group.

Discussion

Our study demonstrated that fentanyl decreased the transfer of small hydrophilic molecules across the BBB (decreased K_i and decreased permeability-surface area product) despite a lack of significant change in the average cerebral flow with fentanyl.

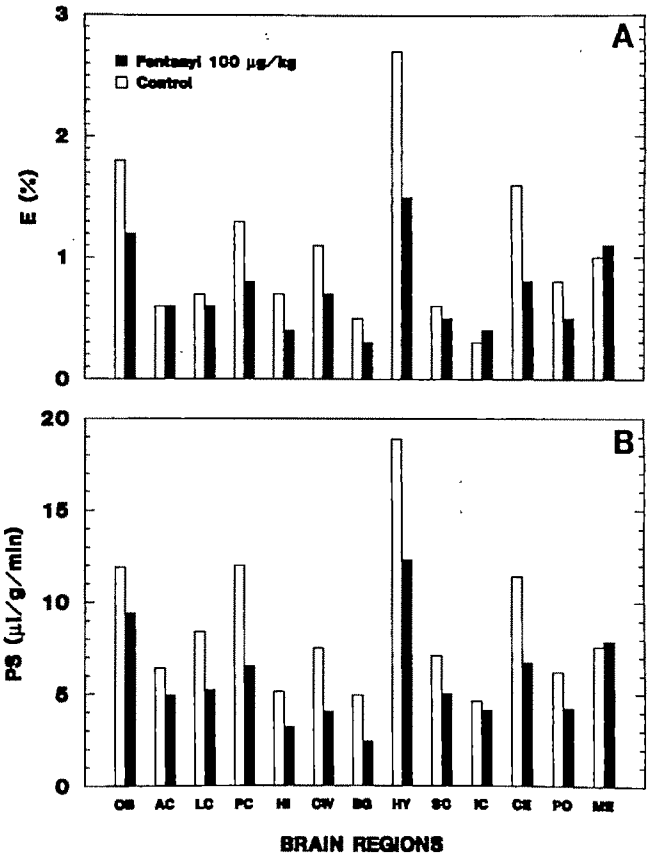


Figure 3. (A) Regional extraction fraction (E) in examined regions of the control and the high-dose fentanyl groups. (B) Regional permeability-surface area (PS) product. Abbreviations as in Figure 1.

This decrease may be related to a direct effect of fentanyl on the permeability of the BBB or a reduction in the perfused capillary surface area, or both.

Extreme hypertension or extreme hypotension, especially in combination with vasodilators, may alter the permeability of the BBB (4,5). The mean blood pressures during fentanyl administration were not different from those in the control animals. Therefore, it is unlikely that blood pressure had any effect on permeability in our study. Extreme hypercapnia caused by prolonged breathing of 25% CO_2 may open the BBB (15,16); however, $Paco_2$ in the fentanyl groups was not significantly different from that in the control group.

Over the range of rCBF reported in this study, the permeability-surface area product should be independent of flow (17,18). The transfer of lipid-soluble compounds across the BBB is flow limited as well as permeability dependent, which makes lipid soluble compounds less suitable for BBB permeability studies (19). For this reason, AIB, an inert hydrophilic molecule was used to measure K_i in our study. The rCBF in the high-dose fentanyl group was not significantly

different from that in the control group. Effects of rCBF on K_i were probably not important in our study.

Saija et al. (7) suggested that brain metabolism may affect K_i. They reported that K_i for ^{14}C-AIB significantly decreased during pentobarbital and ketamine anesthesia. It was suggested that pentobarbital-induced decreases in neuronal activity or metabolism may be the reason for this decrease. In support of this hypothesis, an external stimulus such as a high-intensity light is known to increase the transport across the BBB in the occipital cortex (20). Stress may also modify the vascular permeability of the brain, presumably through the altered release of neurotransmitters (21). Ketamine, despite increased glucose utilization, decreased K_i in the study of Saija et al. (7). They explained this phenomenon with another hypothesis; i.e., ketamine caused vasoconstriction at the level of cerebral microcirculation (22).

In the present study, K_i was decreased at our low dose of fentanyl and did not show any further change at the higher dose. In comparison, Carlsson et al. (23) reported that fentanyl produced a linear decrease in cerebral O_2 consumption in rats until 100 μg/kg of fentanyl was administered. This was a maximal reduction because there were no further changes above this dose in rats without the appearance of seizures (23). In dogs, this high dose of fentanyl had little effect on cerebral O_2 consumption (24). It is therefore difficult to say that the decrease of K_i at the low dose of fentanyl is mainly due to the decreased metabolism during fentanyl anesthesia. A similar phenomenon occurred during isoflurane anesthesia; i.e., K_i did not decrease any further after 1% isoflurane, as demonstrated in our previous study (8).

The action of fentanyl on the regional permeability-surface area product may be related to its effect on the perfused capillary surface area. At similar rCBF, alteration of experimental conditions may change the number, volume, or surface area of perfused cerebral capillaries (25,26). A decrease in the perfused capillary surface area may be partially related to reduced cerebral metabolism. Metabolites such as adenosine or K^+ play an important role in controlling the terminal arteriole and precapillary sphincters (27). Fentanyl may affect the vascular tone through its actions on neuronal function because cerebral vessels are richly innervated. In addition, fentanyl may have some direct effects on the vascular tone that may decrease the perfused capillary surface area.

Permeability itself may also be affected by fentanyl. Rapoport (28) demonstrated that the osmolal threshold that opens the BBB increased with increasing lipid solubility, as expected from the inverse relation between lipid solubility and cell shrinkage by hypertonic solutions (29,30). Because fentanyl has a high lipid solubility like other anesthetics (31), it may affect the lipid layers of endothelial cells and affect the size or the shape of the cell membrane carrier systems and intercellular tight junctions. It could be hypothesized that all centrally acting lipophilic agents would decrease K_i. Fentanyl may also directly affect cell membrane carrier systems at the BBB. These hypotheses may partially explain the decrease of K_i despite increased glucose metabolism under ketamine anesthesia in the study by Saija et al. (7).

Our study demonstrated that the transfer of small hydrophilic molecules across the BBB was decreased during fentanyl anesthesia. It is not clear how fentanyl anesthesia decreases the transfer of small hydrophilic molecules across the BBB; however, the decrease of the transfer coefficient of ^{14}C-AIB was not related to changes in blood pressure or in cerebral blood flow. Whether this is an effect on permeability of the BBB or on the surface area of perfused cerebral capillaries caused by fentanyl was not directly determined in our study.

We thank Patricia A. Sheffield, MA, for her expert editorial assistance.

References

1. Bradbury M. The concept of a blood-brain barrier. London: Wiley, 1979:383–407.
2. Pardridge WM. The gate keeper: how molecules are screened for admission to the brain. Science 1987;27:51–5.
3. Neuwelt EA, Maravilla KR, Frenkel EP, Barnett P, Hill S, Moore RJ. The use of enhanced computerized tomography to evaluate osmotic blood brain barrier disruption. Neurosurgery 1980;6:49–56.
4. Forster A, Van Horn K, Marshall LF, Shapiro HM. Anesthetic effects on blood-brain barrier function during acute arterial hypertension. Anesthesiology 1978;49:26–30.
5. Ishikawa T, Funatsu N, Okamoto K, Takeshita H, McDowall DG. Blood-brain barrier function following drug-induced hypotension in the dog. Anesthesiology 1983;59:526–31.
6. Gumerlock MK. Cerebrovascular disease and blood-brain barrier. In: Neuwelt EA, ed. Implications of the blood-brain barrier and its manipulation. New York: Plenum, 1989:495–565.
7. Saija A, Princi P, De Pasquale R, Costa G. Modifications of the permeability of the blood-brain barrier and local cerebral metabolism in pentobarbital- and ketamine-anaesthetized rats. Neuropharmacology 1989;28:997–1002.
8. Chi OZ, Anwar M, Sinha AK, Wei HM, Klein SL, Weiss HR. Effects of isoflurane on transport across the blood-brain barrier. Anesthesiology 1992;76:426–31.
9. Oldendorf WH. Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol 1971;221:1629–39.
10. Blasberg RG, Fenstermacher JD, Patlak CS. Transport of α-aminoisobutyric acid across brain capillary and cellular membranes. J Cereb Blood Flow Metab 1983;3:8–32.
11. Beck T, Krieglstein J. Cerebral circulation, metabolism, and blood-brain barrier of rats in hypocapnic hypoxia. Am J Physiol 1987;252:H504–12.
12. Gross PM, Blasberg RG, Fenstermacher JD, Patlak CS. The microcirculation of rat circumventricular organs and pituitary gland. Brain Res Bull 1987;18:73–85.

13. Sakurada O, Kennedy C, Brown JD, Carbin OL, Sokoloff L. Measurement of local cerebral blood flow with iodo-C^{14}-antipyrine. Am J Physiol 1978;234:H59–66.
14. Cremer JE, Cunningham VJ, Seville MP. Relationship between extraction and metabolism of glucose, blood flow, and tissue blood volume in regions of rat brain. J Cereb Blood Flow Metab 1983;3:291–302.
15. Freygang WH Jr, Sokoloff L. Quantitative measurement of regional circulation in the central nervous system by the use of radioactive inert gas. Adv Biol Med Phys 1958;6:263–79.
16. Møllgård K, Sørensen SC. Changes in capillary permeability in the brain studied with alcian blue as a tracer. Acta Physiol Scand Suppl 1973;396:12.
17. Bradbury MW. Transport across the blood-brain barrier. In: Neuwelt EA, ed. Implications of the blood-brain barrier and its manipulation. Volume 1: Basic science aspects. New York: Plenum, 1989:119–36.
18. Smith QR. Quantitation of blood-brain barrier permeability. In: Neuwelt EA, ed. Implications of the blood-brain barrier and its manipulation. Volume 1: Basic science aspects. New York: Plenum, 1989:85–118.
19. Crone C, Levitt DG. Capillary permeability to small solutes. In: Renkin EM, Michel CC, eds. Handbook of physiology. Section 2: The cardiovascular system. Volume 4: Microcirculation. Part 1. Bethesda: American Physiological Society, 1984:411–66.
20. Saija A, Princi P, De Pasquale R, Costa G. High intensity light exposure increases blood-brain barrier transport in rats. Pharmacol Res Commun 1988;20:553–9.
21. Sharma HS, Dey PK. Impairment of blood-brain barrier (BBB) in rat by immobilization stress: role of serotonin (5-HT). Indian J Physiol Pharmacol 1981;25:111–22.
22. Altura BT, Altura BM. Effects of barbiturates, phencyclidine, ketamine and analogues on cerebral circulation and cerebrovascular muscle. Microcirc Endothelium Lymphatics 1984; 1:169–84.
23. Carlsson C, Smith DS, Keykhah MM, Englebach I, Harp JR. The effects of high-dose fentanyl on cerebral circulation and metabolism in rats. Anesthesiology 1982;37:375–80.
24. Milde LN, Milde JH, Gallagher WJ. Cerebral effects of fentanyl in dogs. Br J Anaesth 1989;63:710–5.
25. Grover GJ, Francois-Dainville E, Buchweitz E, Weiss HR. Effect of hemorrhage on regional morphometric indexes of cerebral capillarity. J Appl Physiol 1986;61:1712–9.
26. Buchweitz-Milton E, Weiss HR. Perfused microvascular morphometry during middle cerebral artery occlusion. Am J Physiol 1988;255:H623–8.
27. Paulson OB, Newman EA. Does the release of potassium from astrocyte endfeet regulate cerebral blood flow? Science 1987; 237:896–8.
28. Rapoport SI. Modification of cerebrovascular permeability by hypertonic solutions and conditions which alter autoregulation of cerebral blood flow. In: Cervos-Navarro, ed. The cerebral vessel wall. New York: Raven, Press 1976:215–23.
29. Collander R. The permeability of plant protoplasts to non-electrolytes. Trans Faraday Soc 1937;33:985–90.
30. Overton E. Über die osmotischen Eigenschafter der lebenden Pflanzen und Tierzelle. Vierteljahresschr Naturforsch Ges Zurich 1895;40:159–201.
31. Bailey PL, Stanley TH. Narcotic intravenous anesthetics. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1980:281–366.

Evaluation of the Endotracheal Intubating Conditions of Rocuronium (ORG 9426) and Succinylcholine in Outpatient Surgery

Friedrich K. Pühringer, MD, Karin S. Khuenl-Brady, MD, Johann Koller, MD, and Gottfried Mitterschiffthaler, MD

Clinic for Anaesthesia and General Intensive Care Medicine, University of Innsbruck, Innsbruck, Austria

The time-course of action and tracheal intubating conditions of rocuronium and succinylcholine under intravenous anesthesia with propofol, alfentanil, and nitrous oxide were studied in 30 patients undergoing outpatient surgery. The neuromuscular effects of both drugs were quantified by recording the indirectly evoked twitch response of the adductor pollicis muscle after ulnar nerve stimulation (0.1 Hz, 0.2 ms supramaximal stimuli). Patients were given either 0.6 mg/kg rocuronium ($n = 20$) or 1 mg/kg succinylcholine ($n = 10$) intravenously. Sixty seconds after the administration of the muscle relaxant, the trachea was intubated and the intubating conditions were scored by a "blinded" assessor. Intubating conditions were not different ($P = 0.34$) between the rocuronium and succinylcholine groups. The onset and duration of neuromuscular blockade were shorter with succinylcholine than with rocuronium. The depression of the twitch response to 5% of control value occurred in 0.8 ± 0.1 min with 1 mg/kg succinylcholine and 1.2 ± 0.5 min with 0.6 mg/kg rocuronium ($P < 0.01$). The recovery of the twitch response to 25%, 75%, and 90% of its control value was shorter after succinylcholine ($P < 0.001$) and occurred at 8.1 ± 2.6, 10.3 ± 3.9, 11.3 ± 4.6 and 25.3 ± 5.0, 33.1 ± 5.9, 36.1 ± 6.3 min after succinylcholine and rocuronium, respectively. Also the time required for spontaneous recovery from 25% to 75% of the control twitch response was significantly shorter ($P < 0.001$) after succinylcholine (2.2 ± 1.4 min) than after rocuronium (7.8 ± 2.1 min). It is concluded that in spite of the pharmacodynamic differences between succinylcholine and rocuronium, the intubating conditions after administration of both compounds are similar and develop at the same rate.

(Anesth Analg 1992;75:37–40)

Rocuronium (ORG 9426) is a new, nondepolarizing neuromuscular blocking drug that has been reported to develop optimal tracheal intubating conditions more rapidly than vecuronium (1). In initial clinical studies, the ED_{95} of rocuronium was found to be 0.3 mg/kg (2). Fast onset times resulting in rapid development of optimal tracheal intubating conditions and brief time-course of neuromuscular blockade are of prime importance in outpatient anesthesia. Therefore this study was undertaken to compare tracheal intubating conditions and time-course (onset, duration, and recovery rate) of action of a single bolus dose of 0.6 mg/kg rocuronium ($2 \times ED_{95}$) with those after a single bolus dose of 1 mg/kg succinylcholine ($3 \times ED_{95}$) (3) in outpatients anesthetized with intravenous propofol, alfentanil, and nitrous oxide.

Methods

After approval by the local Medical Ethical Committee, 30 consenting ASA class I or II patients of either sex, of normal weight, between 18 and 65 yr of age, scheduled for surgery up to 1-h duration were included in the study. Patients known or suspected to have neuromuscular disorders, metabolic diseases, or impaired kidney or liver function, patients taking medication known to alter neuromuscular transmission, and women in whom pregnancy could not be excluded did not participate in this trial. In women of childbearing age, the possibility of pregnancy was excluded by a negative HCG Nostick test.

Patients were premedicated with 1 mg/kg meperidine and 0.01 mg/kg atropine IM 1 h before induction of anesthesia. Anesthesia was induced with propofol up to 2.5 mg/kg and alfentanil up to 25 μg/kg IV and

This study was supported in part by a grant from Organon Teknika.

Accepted for publication February 20, 1992.

Address correspondence to Dr. Pühringer, Clinic for Anaesthesia and General Intensive Care Medicine, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Randomization Schedule

Group	Consecutive patients									
1 (1 mg/kg succinlycholine)	1	6	10	13	16	21	24	26	28	30
2 (0.6 mg/kg rocuronium)	2	3	4	5	7	8	9	11	12	14
	15	17	18	19	20	22	23	25	27	29

maintained by controlled ventilation with 2:1 nitrous oxide/oxygen and a continuous intravenous infusion of propofol (4 $mg \cdot kg^{-1} \cdot h^{-1}$) and alfentanil (50 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Then the assessment of neuromuscular transmission was started. Recordings of the single-twitch contractions of the adductor pollicis muscle were obtained by stimulating the ulnar nerve at the wrist through surface electrodes with supramaximal square-wave stimuli of 0.2-ms duration at a frequency of 0.1 Hz. The resultant force of thumb adduction was quantified via a force displacement transducer after applying a resting tension of 200–400 g and recorded. During determination of the maximal twitch response and the supramaximal stimulation current, ventilation was controlled. After a stable twitch response (no change in the twitch height at the same stimulation current) was obtained for a period of at least 3 min (control twitch tension), the patients received at random (Table 1) either 0.6 mg/kg ($2 \times ED_{95}$) of rocuronium or 1 mg/kg ($3 \times ED_{95}$) succinylcholine.

Skin temperature (above the thenar) and the esophageal temperature were monitored continuously using appropriate probes. Body and hand temperatures were kept within a range of less than 0.5°C at 36.5°C and 32.5°C, respectively.

Approximately 60 s after administration of the muscle relaxant, the intubating conditions were assessed always by the same experienced anesthesiologist who performed tracheal intubation thereafter. This person was unaware of the twitch response at the time of laryngoscopy, unaware of the muscle relaxant used, and not in charge of the anesthetic procedure. Intubation conditions were scored as excellent (good jaw relaxation, vocal cords open, no response to intubation), good (good jaw relaxation, vocal cords open but minimal reaction to intubation), poor (moderate jaw relaxation, moving vocal cords, intubation requiring pressure accompanied by coughing and/or bucking), or as inadequate (intubation impossible due to poor jaw relaxation or closed cords). In assessing the neuromuscular effects of rocuronium and succinylcholine, we measured onset time (time from the end of injection until suppression of the twitch tension to 5% of its control value), duration of action (time from the end of injection until recovery of the twitch tension to 25%, 75%, and 90% of control value), and recovery index (time required from 25% to 75% recovery of the twitch tension).

Table 2. Steward Score for Clinical Recovery

Wakefulness	Ventilation	Movements	Points
Not responding	Airway requires maintenance	Not moving	0
Responds to stimuli	Maintaining good airway	Nonpurposeful movements	1
Fully awake	Coughing on command	Moves purposefully	2

Minimum score: 0 points; maximum score: 6 points.

All patients were allowed to recover spontaneously until at least 5 min after the recovery of the twitch response to 90% of its control value. During continuous recording of single twitch, a train-of-four (TOF) stimulation (2 Hz for 2 s) was interposed after induction of the anesthesia and before the administration of the muscle relaxant. Additional TOF tests were done at 25%, 75%, and 5 min after 90% recovery of twitch tension. At the end of anesthesia all patients were scored for their clinical recovery using the Steward scoring system (4) (Table 2). In addition, patients were asked to perform a 5-s head lift after tracheal extubation and again 10 min after arrival in the recovery room.

Neuromuscular data between the two groups were compared using the Student's *t*-test for unpaired data and, when appropriate, the χ^2-test (comparison of intubation conditions and demographic characteristics). Differences were considered significant at $P < 0.05$. All values are given as mean ± SD.

Results

There were no significant differences in the demographic characteristics between the two groups of patients (Table 3). The tracheal intubating dose of both succinylcholine and rocuronium resulted in 100% depression of twitch tension in all patients. Intubating conditions were rated as excellent or good in all patients except one with poor intubating conditions in the succinylcholine group. Table 4 shows that the proportions of patients with excellent or good intubating conditions were not different ($P = 0.34$) in the rocuronium and succinylcholine groups. In one patient in the succinylcholine group and in

Table 3. Demographic Characteristics

Group	Weight (kg)	Height (cm)	Age (yr)	Sex[a]
Succinylcholine				
Mean	67.6[b]	170.1[b]	25.7[b]	4/6[b]
SD	9.8	8.0	6.2	
Range	55–84	160–183	18–38	
Rocuronium				
Mean	65.4[b]	169.6[b]	30.5[b]	11/9[b]
SD	9.3	9.4	8.6	
Range	51–79	154–186	18–49	

[a]M/F.
[b]No significant difference.

Table 4. Intubating Conditions at 1 Minute After Succinylcholine and Rocuronium

	Excellent	Good	Poor	Inadequate
Succinylcholine	8	1	1	0
Rocuronium	17	3	0	0

$P = 0.34$, χ^2-test.

two patients in the rocuronium group—all rated as good—the anesthesiologist performing the intubation noted minor movements in response to laryngoscopy and intubation but was not able to distinguish between the two drugs. The onset time after succinylcholine was significantly shorter than that after rocuronium (0.8 vs 1.2 min). The duration to 25%, 75%, and 90% recovery of the twitch tension to its control value and the recovery index (25%–75% recovery) were significantly shorter ($P < 0.001$) after succinylcholine when compared with rocuronium (Table 5). The TOF ratios (%) after rocuronium at 25% and 75% recovery of the twitch response as well as 5 min after 90% recovery of the twitch tension (final value) are listed in Table 6. No differences could be demonstrated in the overall clinical recovery assessed by the Steward scores. All 30 patients reached the maximal score of six points and were able to perform a 5-s head lift at the end of anesthesia.

Discussion

The results of the present study indicate that rocuronium resembles succinylcholine in producing good-to-excellent intubating conditions approximately 1 min after its administration. In a similar (5) clinical study, the 1-min intubating conditions seemed to be indistinguishable after rocuronium (0.6 mg/kg) and succinylcholine (1.5 mg/kg) preceded by gallamine 10 mg. It is conceivable, therefore, that rocuronium might affect the vocal cords and probably other laryngeal muscles more rapidly than the adductor pollicis muscle. This could explain why the above two muscle relaxants showing significantly different onset times at the adductor pollicis muscle produce, at comparable rates, neuromuscular block of sufficient magnitude for good-to-excellent intubating conditions.

Adhering to the clinical practice, in this study we have used the standard intubating doses of both compounds. However, these conditions probably favored the rate of block development after succinylcholine as the standard intubating dose of this drug (1.0 mg/kg, 3 × ED_{95}) is larger than that of rocuronium (0.6 mg/kg, 2 × ED_{95}). Differences in neuromuscular blocking potency and in the rate of block development between the skeletal muscle and the vocal cords with other muscle relaxants have been reported both in animal and humans. Donati and coworkers (6) were able to demonstrate with vecuronium more rapid block development on the vocal cords than on the adductor pollicis muscle in anesthetized patients. In the cat, succinylcholine (7), *d*-tubocurarine, and atracurium were significantly less potent at the vocal cords than on the tibialis anterior muscle. Our results suggest that the maximal effect after rocuronium at the vocal cords is reached at a rate similar to that of succinylcholine and at a more rapid rate than on the adductor pollicis muscle. Although our observations and also that of others (5) suggest that rocuronium when compared with succinylcholine produced similar intubating conditions at a comparable rate, it should be emphasized that the assessment of intubating conditions is difficult and remains notoriously inaccurate. A "clean" and entirely unbiased comparison with succinylcholine and its fasciculations is even more difficult in spite of all attempts to "blind" the intubating anesthesiologist.

In this study rocuronium produced good-to-excellent intubating conditions at the same rate as succinylcholine; however, its time-course variables including onset time, duration to 25%, 75%, and 90% recovery to control twitch tension, and its recovery index at the adductor pollicis muscle are significantly longer than those after succinylcholine. The total duration of action (spontaneous recovery to 90% of the control twitch tension) approximated 36 min in this study. Nevertheless, 25% recovery of the twitch tension is reached in approximately 25 min after the administration of rocuronium. At this point the residual neuromuscular blockade can always be safely reversed whenever necessary (8). In this study, all patients were allowed to recover spontaneously until 5 min after the twitch tension recovered to 90% of its control value. At this time, the last TOF test showed a mean ratio of 0.64 with a wide range of variation of 0.4–0.8 among the patients. In spite of the fact that at

Table 5. Time-Course of Action of Succinylcholine (n = 10) and Rocuronium (n = 20)

	Onset (min)	Recovery to percent of the control twitch tension (min)			Recovery index (min)
		25%	75%	90%	
Succinylcholine	0.8 ± 0.1	8.1 ± 2.6	10.3 ± 3.9	11.3 ± 4.6	2.2 ± 1.4
Rocuronium	1.2 ± 0.5	25.3 ± 5.0	33.1 ± 5.9	36.1 ± 6.3	7.8 ± 2.1
P	<0.01	<0.0001	<0.0001	<0.0001	<0.0001

Onset, time from end of injection to 95% twitch depression; recovery index, time from 25% to 75% recovery of the twitch tension. Values are mean ± SD.

Table 6. Train-of-Four Ratio During Spontaneous Recovery of the Twitch Response After Rocuronium

	TOF ratio at recovery of twitch response to percent of its control		
	25%	75%	90%
Mean	0.04	0.32	0.63
SD	0.05	0.1	0.13
Range	0–0.22	0.1–0.5	0.4–0.8

TOF, train-of-four.

the end of the anesthesia the TOF ratio was less than 0.7, there was no clinical need for reversal in any of the patients. Before leaving the operating room, the maximal score in the Steward score was reached in all patients and all patients were able to perform a 5-s head lift. Although the Steward score does not evaluate the recovery of the muscle strength specifically, it includes the assessment of coughing on command.

We conclude that in this study the intubating conditions approximately 60 s after the administration of rocuronium were satisfactory and similar to those observed after succinylcholine. The clinical duration of action associated with the intubating dose of rocuronium provides adequate muscle relaxation for the duration of most of the surgical interventions in outpatient cases. The above properties, if confirmed in future studies and in widespread clinical use in a large number of patients, will make rocuronium a suitable alternative to succinylcholine in outpatient anesthesia.

We acknowledge the support and assistance of Dr. Klaus Böheim, Dr. Ulla Riccabona, and Dr. Harald Büchele in this study.

References

1. Witkowsky TA, Bartkowsky RR, Azad SS, Epstein RH, Marr A, Lessin J. ORG 9426, a new short acting muscle relaxant: onset and duration of action (abstract). Anesth Analg 1990;70:S437.
2. Wierda JM, De Wit AP, Kuizenga K, Agoston S. Clinical observations on the neuromuscular blocking action of ORG 9426, a new steroidal non-depolarizing agent. Br J Anaesth 1990;64:521–3.
3. Smith CE, Donati F, Bevan DR. Dose response curves for succinylcholine: single versus cumulative techniques. Anesthesiology 1987;67:A358.
4. Steward DJ. A simplified scoring system for the post-operative recovery room. Can Anaesth Soc J 1975;22:111–3.
5. Huizenga ACT, Vandenbrom RHG, Wierda JMKH, Hommes FDM, Hennis PJ. Intubating conditions and onset time of neuromuscular block of ORG 9426 (rocuronium), a new nondepolarizing neuromuscular blocking agent; a comparison with suxamethonium. Acta Anaesthesiol Scand 1992 (in press).
6. Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and the adductor pollicis. Anesthesiology 1991;74:833–7.
7. Vandenbrom RHG, Howertjes MC, Agoston S. A method for studying the pharmacodynamic profile of neuromuscular blocking agents on vocal cord movements in anaesthetized cats. Br J Pharmacol 1991;102:861–4.
8. Wierda JM, Hennis PJ, De Wit AP, Lambalk LM, Kleef UW, Agoston S. Pharmacodynamic and pharmacokinetic studies with ORG 9426. In: Proceedings of the David Savage Memorial Interface Symposium. Amsterdam: Excerpta Medica, 1990:182–93.

Intraoperative Patient-Controlled Analgesia: An Alternative to Physician Administration During Outpatient Monitored Anesthesia Care

John Zelcer, FFARACS, Paul F. White, PhD, MD, FFARACS, Steven Chester, FFARACS, John D. Paull, FFARACS, and Rowan Molnar, MB, BS

Department of Anesthesia, Royal Women's Hospital, Melbourne, Australia and Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas

Outpatients undergoing minor diagnostic and therapeutic procedures associated with intermittent discomfort are frequently given bolus injections of intravenous opioid analgesics. In a group of 80 healthy women undergoing vaginal ovum pickup procedures, we evaluated patient-controlled administration of alfentanil using a patient-controlled analgesia device (with a lockout interval of 3 min) as an alternative to conventional physician-controlled administration. The two alfentanil administration techniques were equally effective in providing intraoperative analgesia. The average alfentanil dosage requirements were 1.49 ± 0.50 and 1.46 ± 0.55 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± SD) in the physician- and patient-controlled groups, respectively. The incidence of postoperative nausea was the same in both treatment groups (8%). Even with the mandatory lockout interval, intraoperative patient-controlled administration of alfentanil was comparable to physician-controlled administration with respect to patient comfort and satisfaction during vaginal ovum pickup procedures.

(Anesth Analg 1992;75:41–4)

Vaginal ovum pickup (VOPU) procedures are part of the prefertilization protocol for in vitro fertilization. These outpatient procedures involve aspiration of ovum follicles by means of an ultrasonically directed needle passed through the vaginal wall under monitored anesthesia care (MAC). Pain is produced each time the aspiration device penetrates the capsule of the ovary. As the pain associated with transvaginal ovum retrieval is intermittent rather than continuous, the ideal analgesic drug would possess a rapid onset and short duration of effect to allow maximal flexibility and responsiveness to the patient's analgesic needs.

Although fentanyl is commonly administered during these procedures, it requires 3–4 min to achieve its maximal clinical effect after a bolus injection, and it has an elimination half-life of 3–6 h (1). In addition, there is the added risk of profound ventilatory depression when fentanyl is administered in combination with midazolam, a widely used sedative-anxiolytic medication (2). Alfentanil is a faster-acting derivative of fentanyl that has a significantly shorter elimination half-life and is associated with a more rapid recovery of postoperative psychomotor function (3,4). As a result of the rapid onset of action of alfentanil, it may be possible for patients to determine their own needs for this analgesic medication during VOPU procedures by means of a patient-controlled analgesia (PCA) delivery system (5).

Therefore, we designed a randomized, prospective study to evaluate the perioperative effects of alfentanil when administered with either a PCA delivery system or a physician-controlled dosing technique during outpatient VOPU procedures.

Methods

Eighty healthy consenting adult women presenting for outpatient VOPU procedures under MAC were randomly assigned to receive alfentanil by either

This work was supported by a grant from Janssen-Cilag Pty., Ltd., Lane Cove, N.S.W.

An abstract of this article was presented at the 65th Congress of the International Anesthesia Research Society, March 1991, San Antonio, Texas.

Accepted for publication March 11, 1992.

Address correspondence to Dr. White, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9068.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

anesthesiologist-administered or patient-controlled bolus injections. The study protocol was approved by the Human Research Ethics Committee at the Royal Women's Hospital in Melbourne, Australia. Patients with preexisting cardiovascular or pulmonary disease, as well as those whose surgical procedure included a laparoscopy, were excluded from the study.

On arrival in the operating room, an intravenous cannula was inserted and a 5-mL/kg infusion of lactated Ringer's solution was administered over 5 min. All patients were premedicated with midazolam (0.02 mg/kg IV), and oxygen was administered by nasal cannula at a flow rate of 6 L/min throughout the procedure. Routine monitors included a pretracheal stethoscope, noninvasive blood pressure device, electrocardiograph, pulse oximeter, and capnograph (connected to a cannula placed in the nose).

After obtaining baseline values for the hemodynamic and respiratory variables, all patients received a loading dose of alfentanil (10 μg/kg IV) over 1–2 min. Maintenance bolus doses of alfentanil (5 μg/kg IV) were then administered either by the anesthesiologist or by the patient using a PCA delivery system (Graseby Medical Ltd., Watford, U.K.) with a minimal lockout interval of 3 min. The intraoperative alfentanil requirement was assessed by analyzing the number of supplemental bolus doses administered as well as the number of patient demands. Mean arterial blood pressure, heart rate, respiratory rate, and oxygen saturation were recorded at 1–2-min intervals during the procedure.

On arrival in the postanesthesia care unit (PACU), patients were asked to assess their overall level of pain during the procedure by means of a 100-mm linear analogue scale (0 = none to 100 = severe). Their overall level of comfort during the procedure was also scored by a six-point scale: 1, very comfortable; 2, comfortable; 3, uncomfortable; 4, very uncomfortable; 5, painful; and 6, very painful. Postoperative side effects (and therapy required) were recorded by the PACU staff who were unaware of the analgesic treatment group. Antiemetic drugs were used to treat protracted nausea and vomiting (lasting >15 min). Patient acceptance of their intraoperative analgesic therapy was evaluated at the time of discharge from the PACU by a four-point scale: 1, highly acceptable; 2, acceptable; 3, disappointing; and 4, never again.

Statistical analysis included (a) χ^2-test for analyzing discrete variables (number of bolus doses, discomfort level, side effects); (b) analysis of variance and Student's *t*-test to evaluate the continuous variables (pain analogue scores); and (c) analysis of variance with repeated measures to assess changes in continuous variables during the procedure (mean arterial blood pressure, heart rate, respiratory rate, and oxygen saturation rate values). A P value < 0.05 was considered to represent a significant difference between the two treatment groups.

Table 1. Clinical Characteristics of the Two Alfentanil Analgesic Treatment Groups

	Physician-controlled analgesia (n = 40)	Patient-controlled analgesia (n = 40)
Age (yr)	32 ± 5	34 ± 5
Weight (kg)	63 ± 10	65 ± 13
Baseline vital signs		
MAP (mm Hg)	98 ± 2	95 ± 2
HR (beats/min)	82 ± 2	83 ± 3
RR (breaths/min)	17 ± 0.2	17 ± 0.2
Sao_2 (%)	99.7 ± 0.1	99.9 ± 0.1
Procedure time (min)	18 ± 6	18 ± 6

MAP, mean arterial blood pressure; HR, heart rate; RR, respiratory rate; Sao_2, oxygen saturation.
Results are presented as mean values ± SD.

Table 2. Alfentanil Administration and Dosage Requirements During the Vaginal Ovum Pickup Procedure

	Physician-controlled analgesia (n = 40)	Patient-controlled analgesia (n = 40)
Alfentanil (μg)	1746 ± 647	1730 ± 654
($\mu g \cdot kg^{-1} \cdot min^{-1}$)	1.49 ± 0.50	1.46 ± 0.55
Supplemental bolus (n)	3.4 ± 1.2	3.3 ± 1.3
PCA demands (n)	NA	6.7 ± 4.2

PCA, patient controlled analgesia; NA, not applicable.
Results are presented as mean values ± SD.

Results

Demographic data for the two analgesic treatment groups were similar with respect to age, weight, and duration of the surgical procedure (Table 1). Alfentanil dosage requirements were also similar in the physician- and patient-controlled groups (Table 2). Baseline and intraoperative heart rate, mean arterial blood pressure, respiratory rate, and oxygen saturation values were unchanged both within (i.e., during the procedure) and between treatment groups. Additionally, there were no clinically significant intraoperative side effects in either of the treatment groups. Although patients made significantly more demands than the number of delivered bolus doses in the PCA group (Table 2), there were no differences in the number of supplemental bolus doses between the two groups.

Finally, patient comfort levels and average pain

Table 3. Postoperative Assessment After the Vaginal Ovum Pickup Procedure

	Physician-controlled analgesia (n = 40)	Patient-controlled analgesia (n = 40)
Comfort[a]	2.2 ± 0.9 (2; 1–5)	2.3 ± 1.0 (2; 1–5)
Pain score (mm)	25 ± 15	29 ± 18
Nausea (%)	8	8
Vomiting/retching (%)	0	3
Antiemetic therapy (%)	5	3
Acceptability[b]	1.5 ± 0.5 (1; 1–2)	1.4 ± 0.5 (1; 1–3)

[a]Comfort score: 1, very comfortable to 6, very painful; mean values ± SD (median; range).
[b]Acceptability score: 1, highly acceptable to 4, never again; mean values ± SD (median; range).

scores during the procedure were identical in the two treatment groups (Table 3). Patients in both groups were highly satisfied with their intraoperative analgesia and experienced a low incidence of postoperative emetic sequelae. All patients were discharged within 2 h after arriving in the PACU.

Discussion

Patient-controlled analgesia has become a widely accepted technique for managing acute pain in the postoperative period (5). As patients undergoing minor outpatient diagnostic and therapeutic procedures under MAC may experience transient discomfort not relieved by local anesthesia, we designed a study to evaluate an intraoperative PCA technique using the rapid- and short-acting opioid analgesic alfentanil. Our preliminary data suggest that even with a mandatory 3-min lockout interval, intraoperative alfentanil PCA was as effective as physician-controlled techniques for this outpatient procedure.

In a recently published article, Park and Watkins (6) reported that patient-controlled sedation using a combination of midazolam and fentanyl was a safe and effective technique during epidural anesthesia. Because the use of a fixed-dose sedative-opioid combination will increase the risk of respiratory depression (2), we administered a low dose of midazolam to decrease anxiety without producing drowsiness. We believed that excessive midazolam-induced sedation could interfere with the patient's ability to use the PCA device. After a loading dose of the opioid analgesic, the physician or patient administered supplemental bolus doses of alfentanil on an "as needed" basis during these brief outpatient procedures. Although the number of delivered doses was limited because of the lockout interval in the PCA group, a similar number of supplemental doses were administered in both groups.

The incidence of postoperative nausea or vomiting, or both, was low (8%) with these two alfentanil-based MAC techniques, compared with 54% when the procedure was performed under general anesthesia (7). No other clinically significant side effects were noted during the perioperative period. Overall, patient acceptance scores were high with both the physician- and self-administration techniques; however, the ratio of demanded-to-delivered doses suggests that the PCA group might have experienced better pain control with additional bolus doses of the analgesic. Although it is possible that analgesia could have been improved in the PCA group by decreasing (or eliminating) the mandatory lockout interval between successive bolus doses, it might have increased the incidence of opioid-related side effects (e.g., respiratory depression and nausea and vomiting).

The results of this preliminary study can be criticized because of the subjective criteria (i.e., patient complaints of pain) used to determine the need for additional alfentanil by the anesthesiologists and the mandatory lockout interval, which limited the number of patient-administered doses in the PCA group. In addition, because we were unable to perform this study in a double-blind fashion, both investigator and patient bias could have influenced these results. When patients self-administer the analgesic medication (i.e., PCA), they may be less critical of its overall effectiveness. Finally, the size of the bolus dose, as well as the duration of the lockout interval between successive doses of the analgesic medication in the PCA group, could have altered our findings.

In conclusion, intraoperative PCA with alfentanil is an effective alternative to physician-administered techniques with respect to patient comfort and satisfaction during VOPU procedures. The outcome of this study might have been different if alternative PCA parameters or physician criteria had been used for administering supplemental alfentanil. Further studies are needed to define the role of intraoperative PCA during other diagnostic and therapeutic procedures performed under MAC.

The authors acknowledge the valuable assistance and support of Reta Svans, MS.

References

1. Andrews CJH, Prys-Roberts C. Fentanyl—a review. In: Bullingham RES, ed. Clinics in anesthesiology. London: WB Saunders, 1983;97–122.
2. Bailey PL, Pace NL, Ashburn MA, Moll JWB, East KA, Stanley TH. Frequent hypoxemia and apnea after seda-

tion with midazolam and fentanyl. Anesthesiology 1990;73: 826–30.
3. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62:234–41.
4. White PF, Coe V, Shafer A, Sung M-L. Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesthesiology 1986;64:100–6.
5. White PF. Use of patient-controlled analgesia for management of acute pain. JAMA 1988;259:243–7.
6. Park WY, Watkins PA. Patient-controlled sedation during epidural anesthesia. Anesth Analg 1991;72:304–7.
7. Patasky AO, Kitz DS, Andrews RW, Lecky JH. Nausea and vomiting following ambulatory surgery: are all procedures created equal (abstract)? Anesth Analg 1988;67: S163.

Efficacy of the FEF Colorimetric End-Tidal Carbon Dioxide Detector in Children

Jeffrey S. Kelly, MD, Randall D. Wilhoit, MD, Raeford E. Brown, MD, and Robert James, MS
Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina

Direct laryngoscopy and observation of endotracheal tube (ETT) passage between the vocal cords remain the criterion standard for verifying endotracheal intubation. Detection of end-tidal carbon dioxide ($ETco_2$) serves as an invaluable adjunct to confirm endotracheal intubation, detect inadvertent esophageal intubation, and monitor for accidental tracheal extubation. Capnography, however, is often unavailable outside the operating suite. A commercially available, disposable, colorimetric $ETco_2$ detector (FEF, Fenem, Inc., New York, N.Y.), in which color changes using a numerical scale semiquantitatively measure percent carbon dioxide in exhaled gases, has proved effective in confirming endotracheal intubation in adults, but has not been thoroughly investigated in children. We studied 20 otherwise healthy children, aged 6 mo to 8 yr, with simultaneous infrared and colorimetric $ETco_2$ measurements during elective general anesthesia to evaluate the efficacy of the colorimetric detector. Two hundred of 200 tracheally intubated positive-pressure breaths and 198 of 200 breaths under spontaneous mask ventilation demonstrated a yellow color change (color level 5 or 6), signifying an $ETco_2 \geq 15$ mm Hg (2.0 kPa). Repeated-measures analysis of variance revealed no significant differences in infrared $ETco_2$ values between the two yellow color levels throughout the study period. The associations among color level, infrared $ETco_2$ determinations, ETT size, and ETT "leak" pressures estimated by Spearman rank correlation analysis were significant only for higher infrared $ETco_2$ values with higher ETT leak pressures ($P < 0.05$). No complications were observed. The Fenem disposable colorimetric $ETco_2$ detector effectively confirms clinical signs of endotracheal intubation in children when capnography is unavailable. It may also prove useful in monitoring the adequacy of bag-valve-mask ventilation in these patients.
(Anesth Analg 1992;75:45–50)

Unrecognized esophageal intubation is the single most critical incident associated with catastrophic anesthetic outcome (1). Direct laryngoscopy and clinical evaluation for appropriate endotracheal intubation are most reliably confirmed by measurement of end-tidal carbon dioxide ($ETco_2$) (2), and $ETco_2$ monitoring is rapidly becoming a standard of care in anesthesia practice (3–6). It may not be cost effective in smaller community hospitals, however, to use $ETco_2$ monitoring routinely in sites remote from the operating room, such as the radiology suite, intensive care unit, emergency department, or emergency resuscitation teams.

An inexpensive, disposable, colorimetric $ETco_2$ detector (FEF, Fenem, Inc., New York, N.Y.) has recently become commercially available (7). Whereas many studies have proven the colorimetric $ETco_2$ ($C\text{-}ETco_2$) detector to be sensitive and specific in confirming endotracheal intubation in hemodynamically stable adults (8–12), no published series document the efficacy of the Fenem detector in confirming endotracheal intubation in children. Short expiratory times and small exhaled lung volumes coupled with uncuffed endotracheal tube (ETT) use (with subsequent "leakage" of exhaled gases directly into the oropharynx) may make the $C\text{-}ETco_2$ detector ineffective in this population. We therefore conducted a study to determine the effectiveness of this disposable $C\text{-}ETco_2$ detector in children under controlled anesthetic conditions.

Methods

Following approval by our institution's research practices committee, 20 healthy pediatric patients, aged 6 mo (>50-wk postconceptual age) to 8 yr, undergoing elective surgical procedures, were studied. Parental informed consent was obtained in each case during preanesthetic assessment. Patients were excluded if they had a history of significant cardiopulmonary

Presented in part at the annual meeting of the American Society of Anesthesiologists, October 1991, San Francisco, California.
Accepted for publication February 20, 1992.
Address correspondence to Dr. Kelly, Department of Anesthesia, Bowman Gray School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1009.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

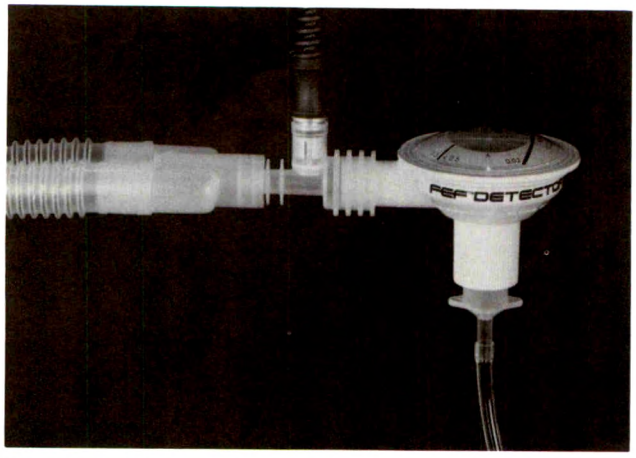


Figure 1. Relationship of patient ETT, Fenem disposable end-tidal CO_2 detector, IR sidestream capnograph adaptor, and anesthesia circuit.

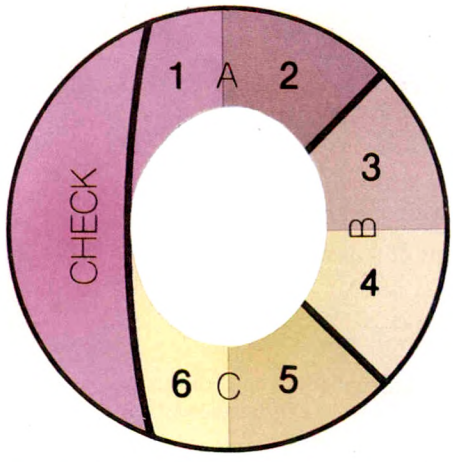


Figure 2. The six-point colorimetric $ETco_2$ scale with respective numerical values as follows: dark purple and light purple (color scales 1 and 2) indicate <3.8 mm Hg CO_2 (<0.5 kPa); dark brown and light brown (color scales 3 and 4) indicate 3.8–15 mm Hg CO_2 (0.5–2.0 kPa); dark yellow and light yellow (color scales 5 and 6) indicate >15 mm Hg CO_2 (>2 kPa). Points A, B, and C represent an alternative measurement scale.

disease or if their anesthetic plan did not include elective endotracheal intubation. Premedication with oral or nasal midazolam was administered as needed, followed by mask induction with halothane, nitrous oxide, and oxygen, using a pediatric circle system. Routine monitors included a pulse oximeter, electrocardiogram, automatic blood pressure cuff, precordial stethoscope, axillary skin temperature probe, peripheral nerve stimulator, intravenous line, and infrared (IR) capnography (Nellcor N-1000 Multifunction Monitor, Nellcor Inc., Hayward, Calif.; 10%–90% response time 85 ms, sample aspiration rate 50 mL/min).

The Fenem detector (7,13) consists of a nontoxic, pH-sensitive chemical indicator strip within a clear plastic dome that reversibly changes color on a breath-to-breath basis depending on the concentration of CO_2 present in the exhaled gases (Figures 1 and 2). The device weighs 18.5 g, contains 38 mL of dead space, and has a shelf life of approximately 15 mo (7). Preliminary evidence suggests that the C-$ETco_2$ detector depends primarily on CO_2 concentration rather than exhaled tidal volume (14,15) and retains its sensitivity with tidal volumes as low as 50 mL when $ETco_2$ values are > 15 mm Hg (2.0 kPa) (15). The average minimum CO_2 concentration required to cause a detectable color change is 4.1 mm Hg (0.54 kPa) (16). The C-$ETco_2$ detector's clinical lifespan is 15–30 min with active circuit humidification and can extend up to 5 h in the absence of these conditions (17,18).

The colorimetric changes measured by the C-$ETco_2$ detector were compared on a breath-by-breath basis with IR-$ETco_2$ readings at two points in the patient's anesthetic course:

1. During surgical anesthetic conditions under spontaneous mask ventilation (i.e., before institution of neuromuscular blockade and endotracheal intubation; study point 1).
2. After establishment of neuromuscular blockade, endotracheal intubation under direct visualization with an uncuffed ETT, clinical confirmation of appropriate ETT position, and institution of controlled positive-pressure ventilation (study point 2).

During both study periods, the C-$ETco_2$ detector was placed in series with the sidestream capnograph adaptor and inserted between the patient's mask or ETT and the circle system Y-connector (Figure 1). Single-breath color changes using a six-point scale (Figure 2) and IR-$ETco_2$ measurements were simultaneously recorded for 10 breaths at each study point by two blinded observers. For the purposes of this study, a false-negative result at study point 2 was defined as a purple or brown color reading (i.e., color levels 1–4) with a simultaneously measured IR-$ETco_2$ value ≥ 20 mm Hg (2.7 kPa). We arbitrarily chose this level of IR-$ETco_2$ to allow a comfortable margin above the $ETco_2$ threshold for brown-to-yellow color change (15 mm Hg, 2.0 kPa). The pressure at which a leak around the uncuffed ETT occurred (cm H_2O pressure) was determined in a double-blind fashion by one observer gradually closing the circle system popoff valve and observing the anesthesia circuit pressure gauge while a second observer listened for air egress with a stethoscope placed at the suprasternal notch. This maneuver was repeated twice in each patient and the values averaged.

Repeated-measures analysis of variance was used to assess differences in IR-$ETco_2$ values between the

Table 1. Demographic Data of Study Population

		Age (mo)		Weight (kg)	
Gender	*n*	Mean	Range	Mean	Range
Female	10	46.3	6.1–82.2	16.1	7.0–23.0
Male	10	51.4	6.2–86.3	16.2	6.4–30.9
Total	20	48.8	6.1–86.3	16.15	6.4–30.9

Table 2. Summary of Study Results

Study point	Color level	No. of breaths	Mean $ETco_2 \pm SD$ (mm Hg)	$ETco_2$ range (mm Hg)
1	1–3	0	—	—
	4	2	17.0 ± 9.9	10–24
	5	134	29.5 ± 6.0	10–43
	6	64	31.7 ± 6.3	18–43
2	1–4	0	—	—
	5	106	37.0 ± 1.5	26–48
	6	94	37.2 ± 1.5	24–48

$ETco_2$, end-tidal carbon dioxide tension; SD, standard deviation.

Table 3. Study Point 1 Results

Breath	Color level median	Capnograph Mean ± SD	Capnograph Range
1	5.0	30.30 ± 6.24	18–41
2	5.0	29.55 ± 5.33	17–38
3	5.0	29.60 ± 6.38	16–41
4	5.0	29.30 ± 7.33	10–40
5	5.0	29.95 ± 7.35	10–40
6	5.0	30.40 ± 5.81	18–39
7	5.0	29.95 ± 5.93	18–40
8	5.5	30.70 ± 6.43	18–43
9	5.0	30.35 ± 6.60	18–43
10	5.5	30.90 ± 6.58	19–43

$C\text{-}ETco_2$ color levels at both study points. Spearman rank correlations were also calculated for study point 2 to estimate the associations among color level, $IR\text{-}ETco_2$, ETT size, and ETT leak pressure. The median within-patient color level and the mean within-patient $IR\text{-}ETco_2$ were used in this analysis. A P value of <0.05 was considered significant.

Results

Demographic data of the study population are shown in Table 1, with study results summarized in Tables 2–4. Median age was 4 yr. Endotracheal tube size at study point 2 ranged from 3.5 to 5.5 mm, with an average ETT leak pressure of 18.6 cm H_2O (range 10–40 cm H_2O).

Of 400 study breaths, 398 registered in the yellow color range (color levels 5 or 6), with the two remaining breaths falling into the brown color range (color level 4). Both color level 4 readings occurred under spontaneous mask ventilation during study point 1 and were easily corrected by adjustment of the patient's face mask. Repeated-measures analysis of variance demonstrated no statistically significant differences in $IR\text{-}ETco_2$ values between color levels 5 and 6 at either study point. A residual analysis was performed on the repeated measures to verify the normality assumptions. Residuals were found not to deviate significantly from normality ($P = 0.786$). Spearman rank correlation analysis revealed significance only between mean $IR\text{-}ETco_2$ and ETT leak pressure, i.e., the higher the leak pressure, the higher the measured $IR\text{-}ETco_2$. While none of the 200 intubated positive-pressure breaths registered in color levels 1–4 (i.e., a false-negative result), we can be 95% confident that the chance of this occurring based on our results is no greater than $3/n$ or 1.5% (19).

Table 4. Study Point 2 Results

Breath	Color level median	Capnograph Mean ± SD	Capnograph Range
1	5.0	37.65 ± 5.80	24–48
2	5.0	37.85 ± 5.60	26–48
3	5.5	37.10 ± 5.74	24–48
4	5.0	37.15 ± 5.22	26–47
5	5.0	37.25 ± 4.96	27–46
6	6.0	37.30 ± 4.81	30–45
7	6.0	37.05 ± 4.44	30–44
8	5.0	36.85 ± 4.46	29–45
9	5.0	36.50 ± 4.57	28–45
10	5.5	36.35 ± 4.55	30–45

No complications or inadvertent esophageal intubations occurred at any time during the study. Spontaneous mask ventilation with the $C\text{-}ETco_2$ detector was well tolerated in all patients without clinical evidence of respiratory distress, decreasing oxygen saturation readings, or hemodynamic instability.

Discussion

Esophageal intubation remains a significant complication of anesthetic care. Cheney and colleagues (1) retrospectively reviewed a series of closed anesthetic malpractice claims and found this event to be the single occurrence most closely associated with death or debilitating injury. A preliminary report also derived from the ASA Closed Claims Study revealed that 41 of 624 total claims (excluding tooth injury) involved esophageal intubation. The ETT was considered properly placed by usual clinical criteria in more

than half of these cases (20). Another retrospective review of more than 163,000 anesthetics discovered 27 cardiac arrests resulting from anesthesia. Inadequate ventilation was thought to be the cause of 12 arrests, 11 of which were deemed avoidable. Unrecognized esophageal intubation accounted for 4 of the 12 episodes (21).

Many studies have documented the usefulness of $ETco_2$ measurement in confirming the clinical observation of the ETT passing into the trachea under direct vision (22–26). Whereas $ETco_2$ detection can occur during esophageal intubation (i.e., a false-positive result), statistically significant and easily discernible carbon dioxide (CO_2) washout to readings ≤15 mm Hg (2.0 kPa) occurs within 10 breaths regardless of how CO_2 is introduced into the stomach (24–29). Capnography is also superior to oxygen saturation measurement in discriminating esophageal intubation from endotracheal intubation, especially in patients preoxygenated with 100% oxygen (23,30). The emergence of capnography as a standard of care in anesthesia practice is evidenced by a proposed modification to the American Society of Anesthesiologists' Standards for Basic Intra-Operative Monitoring stating that ETT position "must be verified by clinical assessment and by the identification of carbon dioxide in the expired gas" (3,4), as well as recent legislative mandates by two states that require continuous $ETco_2$ monitoring for all patients receiving general anesthesia (5,6). However, supplying capnography to sites remote from the operating room is not cost effective for many institutions.

Accurate determination of $ETco_2$ in the pediatric patient presents the clinician with a different set of problems. Increases in dead space to tidal volume ratios, fast respiratory rates, small exhaled tidal volumes, high fresh gas flows, high sidestream capnograph sampling rates, and leakage of exhaled gases around the uncuffed ETT into the oropharynx interact variably to adversely affect qualitative and quantitative $ETco_2$ measurements in children. Badgwell and colleagues (31) have shown that proximal $ETco_2$ measurement accurately reflects $Paco_2$ in all pediatric patients ventilated with a nonrebreathing circuit. This relationship also held true for patients weighing more than 8 kg who were ventilated with a partial rebreathing (Mapleson D) circuit, but not in children under 8 kg. Another study of 27 intubated neonatal ICU patients by McEvedy et al. (32) concluded that distal $ETco_2$ levels more accurately approximate $Paco_2$ than do proximal $ETco_2$ determinations. Preliminary evidence suggests that sidestream capnography aspirated from the middle of the ETT does not differ significantly from proximal IR flow-through $ETco_2$ measurements when using a partial rebreathing circuit in neonates and infants (33). Animal data by Rich and associates (34) clearly demonstrate that the change in $ETco_2$ between the distal tip and the 15-cm mark of a 3.0-mm ETT is < 2 mm Hg and is independent of fresh gas flow and ventilatory mode. More recent work indicates that sidestream capnography using a Nellcor N-1000 (as was used in our study) is accurate in healthy infants under controlled volume ventilation with normal fresh gas flows (35).

Despite its proven usefulness in adults (8–12), laboratory data suggesting its potential efficacy in children (14–16,36), and case reports of successful use of the device (13,37), the C-$ETco_2$ detector has not been systemically evaluated in pediatric patients. Our study confirms the effectiveness of the C-$ETco_2$ detector in children, demonstrating that a yellow color reading corresponds to clinically expected IR-$ETco_2$ measurements in these patients. Higher IR-$ETco_2$ values with higher ETT leak pressures were found, implying more complete alveolar gas sampling with less egress around the uncuffed ETT under these conditions. In spite of increases in equipment dead space from the patient mask, the C-$ETco_2$ detector also proved effective during spontaneous mask ventilation in children when an appropriate face mask seal was maintained. It thus may serve as a useful monitor for adequacy of mask ventilation in this population in conjunction with the usual clinical observations such as chest excursions and breath sounds. We noted no complications and the C-$ETco_2$ detector was well tolerated in all cases, even in two 6-mo-old patients weighing 6.4 and 7.0 kg.

Our study was designed to assess the chance of a false-negative colorimetric reading from proper endotracheal intubation and did not address the issue of false-positive results from esophageal intubation. We hypothesize, however, that the C-$ETco_2$ detector would accurately detect inadvertent esophageal intubation in children based on the 50-mL tidal volume threshold required for a yellow color reading (15), measured exhaled gastric volumes of only 35 mL in adults (25), and piglet data where 33 esophageal intubations were correctly identified despite cola administration or prior mask ventilation (36). Although we exclusively used a pediatric circle system in our patients, the colorimetric detector is effective when used with self-inflating pediatric resuscitation bags (Dr. Ann Thompson, personal communication). In addition, it appears useful for confirming endotracheal intubation when used with the Jackson-Rees modification of the Ayre's T-piece, despite dilution of expired gas by continuous fresh gas inflow (37). We also excluded children with cyanotic heart disease, in whom diminished pulmonary blood flow can cause an increase in the arterial to end-tidal CO_2 difference and potentially lead to false-negative C-$ETco_2$ read-

ings with endotracheal intubation in these patients (38). The conflicting results obtained using the C-ETco_2 detector during adult cardiopulmonary resuscitation, where pulmonary blood flow is also severely limited, emphasizes the dependent relationship between the C-ETco_2 detector's effectiveness and adequate pulmonary blood flow (10–12,39–42). Further study in these areas is warranted. Finally, concerns about the potential for false-negative C-ETco_2 detector readings in observers with red-green color blindness appear unfounded (43).

In summary, we find the Fenem FEF disposable colorimetric ETco_2 detector to be an excellent tool for confirming endotracheal intubation and monitoring spontaneous mask ventilation in children. Its light weight, disposability, ease of use, and effectiveness make it particularly amenable to use in remote anesthetic sites where capnography is not routinely available, during transport of critically ill pediatric patients, and as an invaluable backup in the event of mechanical failure of capnography during a pediatric anesthetic.

We thank Dr. Donald Prough and Faith McLellan for their editorial assistance and Kim Barnes for her word processing expertise.

References

1. Cheney FW, Posner K, Caplan RA, Ward RJ. Standard of care and anesthesia liability. JAMA 1989;261:1599–603.
2. Birmingham PK, Cheney FW, Ward RJ. Esophageal intubation: a review of detection techniques. Anesth Analg 1986;65:886–91.
3. American Society of Anesthesiologists. Standards for basic intra-operative monitoring. Park Ridge, Ill.: Anesthesia Patient Safety Foundation. Anesthesia Patient Safety Foundation Newsletter 1987;2:3.
4. Eichhorn JH. Further changes in basic monitoring standards proposed: amendments up for vote. Park Ridge, Ill.: Anesthesia Patient Safety Foundation. Anesthesia Patient Safety Foundation Newsletter 1990;5:25,27.
5. Lees DE. New York state regulations to be implemented: work hours, resident supervision, anesthesia monitors mandated. Park Ridge, Ill.: Anesthesia Patient Safety Foundation. Anesthesia Patient Safety Foundation Newsletter 1988;3:17,19.
6. Zeitlin G. From the literature: standards of care and capnography. Park Ridge, Ill.: Anesthesia Patient Safety Foundation. Anesthesia Patient Safety Foundation Newsletter 1991;6:20–1.
7. Strunin L, Williams T. The FEF end-tidal carbon dioxide detector. Anesthesiology 1989;71:621–2.
8. Goldberg JS, Rawle PR, Zehnder JL, Sladen RN. Colorimetric end-tidal carbon dioxide monitoring for tracheal intubation. Anesth Analg 1990;70:191–4.
9. Winston RS, Layon J, Gravenstein N, Gallagher TJ. Detection of esophageal intubation with a new chemical monitor of end-tidal carbon dioxide (abstract). Crit Care Med 1990;18: S216.
10. Ornato JP, Shipley JB, Racht EM, et al. Multicenter study of end-tidal carbon dioxide in the prehospital setting (abstract). Ann Emerg Med 1990;19:452.
11. Anton WR, Gordon RW, Jordan TM, Posner KL, Cheney FW. A disposable end-tidal CO_2 detector to verify endotracheal intubation. Ann Emerg Med 1991;20:271–5.
12. MacLeod BA, Heller MB, Gerard J, Yealy DM, Menegazzi JJ. Verification of endotracheal tube placement with colorimetric end-tidal CO_2 detection. Ann Emerg Med 1991;20:267–70.
13. O'Callaghan JP, Williams RT. Confirmation of tracheal intubation using a chemical device (abstract). Can J Anaesth 1988;35: S59.
14. Symreng T, Sum-Ping JST, Mehta M. Sensitivity of FEF end tidal CO_2 detector (abstract). Anesthesiology 1990;73:A479.
15. Freid EB, Good ML, Bonett S, Gravenstein N. Disposable end-tidal CO_2 detector: tidal volume threshold (abstract). Anesthesiology 1990;73:A464.
16. Jones BR, Dorsey MJ. Disposable end-tidal CO_2 detector: minimal CO_2 requirements (abstract). Anesthesiology 1989;71: A359.
17. Ponitz AL, Gravenstein N, Banner MJ. Humidity affecting a chemically based monitor of exhaled carbon dioxide (abstract). Anesthesiology 1990;73:A515.
18. Feinstein R, White PF, Westerfield SZ III. Intraoperative evaluation of a disposable end-tidal CO_2 detector (abstract). Anesthesiology 1989;71:A461.
19. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249:1743–5.
20. Caplan RA, Posner K, Ward RW, Cheney FW. Respiratory mishaps: principal areas of risk and implications for anesthetic care (abstract). Anesthesiology 1987;67:A469.
21. Keenan RL, Boyan CP. Cardiac arrest due to anesthesia: a study of incidence and causes. JAMA 1985;253:2373–7.
22. Mickelson KS, Sterner SP, Ruiz E. Exhaled Pco_2 as a predictor of endotracheal tube placement (abstract). Ann Emerg Med 1986;15:657.
23. Vaghadia H, Jenkins LC, Ford RW. Comparison of end-tidal carbon dioxide, oxygen saturation and clinical signs for the detection of oesophageal intubation. Can J Anaesth 1989;36: 560–4.
24. Linko K, Paloheimo M, Tammisto T. Capnography for detection of accidental oesophageal intubation. Acta Anaesthesiol Scand 1983;27:199–202.
25. Sum-Ping ST, Mehta MP, Anderton JM. A comparative study of methods of detection of esophageal intubation. Anesth Analg 1989;69:627–32.
26. Sum Ping ST, Mehta MP, Symreng T. Reliability of capnography in identifying esophageal intubation with carbonated beverage or antacid in the stomach. Anesth Analg 1991;73: 333–7.
27. Good ML, Modell JH, Rush W. Differentiating esophageal from tracheal capnograms (abstract). Anesthesiology 1988;69: A266.
28. Sum Ping ST. Esophageal intubation (letter). Anesth Analg 1987;66:483.
29. Garnett AR, Gervin CA, Gervin AS. Capnographic waveforms in esophageal intubation: effect of carbonated beverages. Ann Emerg Med 1989;18:387–90.
30. Guggenberger H, Lenz G, Federle R. Early detection of inadvertent oesophageal intubation: pulse oximetry vs. capnography. Acta Anaesthesiol Scand 1989;33:112–5.
31. Badgwell JM, Heavner JE, May WS, Goldthorn JF, Lerman J. End-tidal Pco_2 monitoring in infants and children ventilated with either a partial rebreathing or a non-rebreathing circuit. Anesthesiology 1987;66:405–10.
32. McEvedy BAB, McLeod ME, Mulera M, Kirpalani H, Lerman J. End-tidal, transcutaneous, and arterial Pco_2 measurements in critically ill neonates: a comparative study. Anesthesiology 1988;69:112–6.
33. Badgwell JM, Heavner JE. End-tidal carbon dioxide pressure in neonates and infants measured by aspiration and flow-through capnography. J Clin Monit 1991;7:285–8.
34. Rich GF, Sullivan MP, Adams JM. Is distal sampling of

end-tidal CO_2 necessary in small subjects? Anesthesiology 1990;73:265–8.
35. Splinter WM, Torsher LC. Measurement of end-tidal Pco_2 in infants: effects of low fresh gas flows and volume-cycled ventilators (abstract). Anesth Analg 1991;72:S273.
36. Bhende MS, Thompson AE, Howland DF. Validity of a disposable end-tidal carbon dioxide detector in verifying endotracheal tube position in piglets. Crit Care Med 1991;19:566–8.
37. Higgins D. Confirmation of tracheal intubation in a neonate using the Fenem CO_2 detector (letter). Anaesthesia 1990;45: 591–2.
38. Burrows FA. Physiologic dead space, venous admixture, and the arterial to end-tidal carbon dioxide difference in infants and children undergoing cardiac surgery. Anesthesiology 1989;70: 219–25.
39. Wright RE, Smith KW, Hayes JK, Smith BK, Peters JL. Evaluation of the Fenem FEF end-tidal CO_2 detector in a dog model of cardiopulmonary resuscitation (abstract). Anesth Analg 1990;70:S443.
40. Mehta MP, Symreng T, Sum Ping JST. Reliability of FEF end-tidal CO_2 detector during CPR (abstract). Anesthesiology 1990;73:A473.
41. Varon AJ, Morrina J, Civetta JM. Use of colorimetric end-tidal carbon dioxide monitoring to prognosticate immediate resuscitation from cardiac arrest (abstract). Anesthesiology 1990;73: A412.
42. Varon AJ, Morrina J, Civetta JM. Clinical utility of a colorimetric end-tidal carbon dioxide detector in emergency intubation (abstract). Anesthesiology 1990;73:A413.
43. Rodgers RC. The FEF carbon dioxide analyser (letter). Anaesthesia 1990;45:591.

Oral Midazolam in Children: Effect of Time and Adjunctive Therapy

B. Craig Weldon, MD, Mehernoor F. Watcha, MD, and Paul F. White, PhD, MD, FFARACS

Department of Anesthesiology, Division of Clinical Research, Washington University School of Medicine, St. Louis, Missouri, and the Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas

The purpose of this study was to determine the influence of timing and concomitant administration of atropine and/or meperidine on the perioperative effects of oral midazolam in children. In 154 healthy children, 1–8 yr old, we studied six oral preanesthetic medication regimens according to a randomized, double-blind protocol. Group A (placebo) received 5 mL of apple juice. The other five groups received medication with apple juice to a total volume of 5 mL, 20–60 min before induction of anesthesia. Group B received atropine (0.02 mg/kg); group C received midazolam (0.5 mg/kg); group D received midazolam (0.5 mg/kg) and atropine (0.02 mg/kg); group E received meperidine (1.5 mg/kg) and atropine (0.02 mg/kg); and group F received meperidine (1.5 mg/kg), atropine (0.02 mg/kg), and midazolam (0.5 mg/kg). The sedative effect of midazolam was maximal 30 min after oral administration. Ninety-five percent of the children who were separated from their parents within 45 min after oral midazolam administration (with or without atropine) had satisfactory separation scores (vs 66% of those separated after 45 min; $P < 0.02$). Midazolam-treated patients were more cooperative with a mask induction of anesthesia compared with non-midazolam-treated children (83% vs 56%). Neither atropine nor meperidine appeared to significantly improve the effectiveness of oral midazolam. No preoperative changes in heart rate, respiratory rate, or hemoglobin oxygen saturation were noted in any of the treatment groups. Finally, oral midazolam did not prolong recovery even after outpatient procedures lasting <30 min. In conclusion, midazolam (0.5 mg/kg) given orally 30–45 min before induction of anesthesia is safe and effective without delaying recovery after ambulatory surgery.

(Anesth Analg 1992;75:51–5)

Preanesthetic medication in children should relieve anxiety, reduce the trauma associated with separation from their parents, and facilitate induction of anesthesia without prolonging the recovery period (1–12). Although various combinations of drugs and routes of administration have been used in children for preanesthetic sedation, the oral route remains the least threatening method of drug administration (4–11). A combination of oral meperidine, diazepam, and atropine has been reported to decrease anxiety and to facilitate induction of anesthesia (7). More recently, oral midazolam, 0.5–0.75 mg/kg, was shown to be an effective preanesthetic medication technique that did not prolong recovery after procedures lasting more than 100 min (9).

This study was designed to determine the effects of timing and concomitant administration of atropine and/or meperidine on the perioperative effects of oral midazolam, when administered as a preanesthetic medication in children undergoing outpatient surgical procedures lasting less than 100 min.

Methods

One hundred fifty-four healthy ASA physical status I or II children between the ages of 1 and 8 yr, who were scheduled to undergo outpatient surgical procedures expected to last less than 100 min, were enrolled in this double-blind, placebo-controlled study. The study was approved by the Human Studies Committee of the Washington University School of Medicine, and written informed consent was obtained from the parents or the legal guardian of each subject. We excluded children in whom the use of sedative, analgesic, anticholinergic, or inhaled anes-

This material was presented in part at the American Society of Anesthesiologists meeting in Las Vegas, Nevada, October 19–23, 1990, and at the International Anesthesia Research Society meeting in San Antonio, Texas, March 9–12, 1991.

Accepted for publication February 20, 1992.

Address correspondence to Dr. White, Department of Anesthesiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9068.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

thetics was contraindicated, and children undergoing emergency surgery.

Patients were randomly assigned to one of six oral preanesthetic medication groups. Group A (placebo) received 5 mL of apple juice; group B 0.02 mg/kg of atropine; group C 0.5 mg/kg of midazolam; group D 0.5 mg/kg of midazolam and 0.02 mg/kg of atropine; group E 1.5 mg/kg of meperidine and 0.02 mg/kg of atropine; and group F 1.5 mg/kg of meperidine, 0.5 mg/kg of midazolam, and 0.02 mg/kg of atropine. Groups B–F received their oral preanesthetic medications in apple juice to a total volume of 5 mL. All observers, as well as the children (and their parents), were unaware of the contents of the oral medication.

Baseline heart rate, respiratory rate, and hemoglobin oxygen saturation values (Nellcor N100 pulse oximeter, Nellcor, Hayward, Calif.) were measured before the administration of the preanesthetic medication and at 15-min intervals until the time the patient was taken into the operating room. The level of sedation was assessed at similar time intervals using a four-point scale: 1 = sleepy/calm, 2 = awake/calm, 3 = awake/anxious, and 4 = very anxious/combative. Patients with a score of 1 or 2 were considered to have a "satisfactory" level of sedation; those with a score of 3 or 4 were considered to be "unsatisfactorily" sedated.

Children were separated from their parents after a period of at least 20 min had elapsed following administration of the preanesthetic medication. At the time of separation, the child's willingness to separate from the parents was evaluated on a different four-point scale with 1 = easy separation; 2 = whimpers but is easily reassured, not clinging; 3 = cries and cannot be easily reassured, but not clinging to parents; and 4 = crying and clinging to parents. Children with scores of 1 or 2 were considered to have had an acceptable separation; those with scores of 3 or 4 were considered to have had difficult separations.

After the patient had entered the operating room, anesthesia was induced with halothane and nitrous oxide in oxygen via a face mask. The quality of the anesthetic induction was evaluated using a four-point scale where 1 = excellent (unafraid, cooperative, accepts mask readily), 2 = good (slight fear of mask, easily reassured), 3 = fair (moderate fear of mask, not calmed with reassurance), and 4 = poor (terrified, crying, combative). Children with scores of 1 or 2 were designated as having had a "satisfactory" acceptance of the face mask; scores of 3 or 4 were considered "unsatisfactory." Cases in which excessive oral secretions interfered with the smooth conduct of anesthesia were noted.

After induction, anesthesia was maintained with nitrous oxide, 60%–70% in oxygen with 0.5%–2.5% of halothane adjusted to maintain hemodynamic stability. If tracheal intubation was required, it was facilitated with atracurium, 0.5 mg/kg IV, and at the end of the operation, neuromuscular blockade was antagonized with neostigmine, 0.07 mg/kg IV, and glycopyrrolate, 0.015 mg/kg IV. The times from the administration of preanesthetic medication to separation from the parents and induction of anesthesia were recorded along with the duration of anesthesia and surgery, the time interval from the discontinuation of the anesthetic until spontaneous eye opening and compliance with verbal commands, and the time to discharge from the postanesthesia care unit (PACU).

Cardiorespiratory variables, and hemoglobin oxygen saturation values were recorded immediately on arrival in the PACU and at 15-min intervals while in the PACU. In addition, a sedation score based on the same four-point scale used to assess preoperative sedation was recorded on arrival in the PACU and subsequently at 15-min intervals until discharge. Postoperative side effects and analgesic and antiemetic requirements were noted by the PACU staff.

Continuous variables were compared with a one-way analysis of variance (ANOVA) and a Scheffè's test for post hoc between-groups comparisons. Fisher's exact and χ^2 tests with Yates' correction were used to analyze discrete variables (e.g., incidence of satisfactory sedation and behavior scores). The effects of time on the sedation scores were analyzed independently using the Friedman test. When appropriate, a Bonferroni correction was applied for multiple comparisons. A P value of <0.05 was considered statistically significant.

Results

There were no significant differences between the six groups with respect to age, weight, gender, ASA physical status, or types of operative procedures (Table 1). The proportion of children requiring tracheal intubation was similar in all groups. There were also no significant differences in baseline heart rate, respiratory rate, hemoglobin oxygen saturation values, or sedation scores before the administration of the preanesthetic medication.

Sedation scores, as well as behavior scores at separation from parents, induction of anesthesia, and in the PACU, were similar in children receiving placebo or atropine (group A versus B). Children receiving midazolam with or without atropine (groups C and D) also had similar sedation and behavioral scores. As atropine did not affect sedation or behavior scores, we combined data from groups C and D into a midazolam group (group M), and groups A and B into a non-midazolam-treated group

Table 1. Demographic Data and Preinduction Mean (±SD) Hemoglobin Oxygen Saturation Values for the Six Preanesthetic Medication Treatment Groups

	A	B	C	D	E	F
Premedicant(s)	Placebo	Atropine	Midazolam	Midazolam + atropine	Meperidine + atropine	Meperidine + atropine + midazolam
Number (*n*)	25	27	29	25	24	24
Age (yr)	3.5 ± 2.1	3.5 ± 1.5	3.5 ± 2.0	3.8 ± 2.0	4.2 ± 4.3	4.0 ± 2.0
Weight (kg)	15.8 ± 6.4	15.6 ± 3.9	16.0 ± 5.5	15.8 ± 4.3	18.1 ± 6.9	16.5 ± 5.1
Gender (M/F)	14/11	16/11	18/11	14/11	12/12	14/10
Hemoglobin oxygen saturation values (%)[a]						
0 Min	98 ± 2 (25)	97 ± 2 (27)	97 ± 1 (29)	97 ± 1 (25)	98 ± 2 (24)	98 ± 2 (24)
15 Min	98 ± 2 (24)	98 ± 2 (27)	97 ± 1 (29)	97 ± 1 (25)	98 ± 2 (24)	98 ± 1 (24)
30 Min	98 ± 2 (16)	97 ± 2 (19)	98 ± 1 (9)	97 ± 2 (17)	98 ± 2 (20)	98 ± 1 (19)
45 Min	98 ± 2 (10)	98 ± 1 (4)	97 ± 1 (4)	99 ± 1 (8)	98 ± 1 (11)	97 ± 2 (8)

[a]Number in parentheses equals the number of subjects at each time point after administration of the study medication.

Table 2. Comparison of the Duration of Surgery and Anesthesia, the Incidence of Satisfactory Sedation, Separation and Induction Scores, and Recovery Data for Children in Treatment Groups N, M, E, and F

	N	M	E	F
Premedicant(s)	Placebo (± atropine)	Midazolam (± atropine)	Meperidine + atropine	Meperidine + atropine + midazolam
Number (*n*)	52	54	24	24
Surgical time (min)	35 ± 53	25 ± 40	26 ± 21	52 ± 56
Anesthesia time (min)	42 ± 57	32 ± 45	35 ± 28	69 ± 66[a]
Oral medication − induction time (min)	41 ± 17	36 ± 19	52 ± 25†	42 ± 16
Satisfactory sedation (%)				
0 Min	20/52 (38%)	11/54 (20%)	10/24 (42%)	9/24 (38%)
15 Min	32/52 (63%)	46/54 (85%)[b]	18/24 (79%)	24/24 (100%)[b]
30 Min	19/35 (57%)	25/26 (96%)[b]	16/20 (80%)	19/19 (100%)[b]
45 Min	10/18 (55%)	8/12 (66%)	8/11 (82%)	5/7 (71%)
60 Min	4/10 (40%)	3/5 (60%)	2/2 (100%)	2/2 (100%)
Separation score (%)	75%	89%	75%	92%[b]
Induction score (%)	56%	83%[b]	67%	92%[b]
Eye opening (min)	17 ± 11[c]	20 ± 13	19 ± 8	22 ± 14
Follows commands (min)	24 ± 11[c]	26 ± 14	25 ± 10	32 ± 17
PACU discharge (min)	29 ± 11[c]	29 ± 18[c]	29 ± 12[c]	40 ± 20

PACU, postanesthesia care unit.

Sedation scores represent the percentage of patients with a satisfactory sedation score and the total number of patients for which data are available at that time interval. Separation and induction scores represent the percentage of patients with satisfactory scores.

[a]$P < 0.05$ vs group M.

[b]$P < 0.05$ vs group N.

[c]$P < 0.05$ vs group F.

(group N) for further statistical analysis (Table 2). There were no significant differences between groups M and N with respect to the duration of anesthesia or surgery.

There were no differences in sedation and behavior scores with respect to time in the non-midazolam-treated patients (group N). In contrast, children who received midazolam with or without atropine (group M) had significantly improved sedation scores at 15, 30, and 45 min after oral administration compared to their baseline values, with a peak sedative effect occurring at 30 min (Table 2). In the combined midazolam treatment group, 95% of the children who were separated from their parents within 45 min of the administration of oral preanesthetic medication had satisfactory separation scores compared with only 66% of those who were separated more than 45 min after midazolam administration (P value < 0.02). Although there was no statistically significant difference between groups M and N in the number of patients who had satisfactory

separation from their parents, children in the midazolam group (group M) had significantly higher (satisfactory) acceptance of the mask at induction compared with the non-midazolam-treated (N) group (83% versus 56%; P value < 0.01). In group N, induction was even more difficult than separation (with 75% experiencing satisfactory separations compared to only 56% satisfactory mask inductions, $P < 0.01$).

Patients receiving meperidine with atropine (group E) had significantly improved sedation scores with time, but the sedation scores in this group did not differ significantly from the scores in the other preanesthetic medication groups (Table 2). Children receiving midazolam in addition to meperidine and atropine (group F) also had significantly improved sedation scores with time. In addition, they had significantly improved behavior scores at separation and induction compared to group N, but did not differ from those receiving midazolam without meperidine (group M).

Finally, there were no significant differences in oxygen saturation values between the various treatment groups during the time from administration of preanesthetic medication to induction of anesthesia, even in children receiving the midazolam-meperidine-atropine combination (Table 1). Excessive oral secretions were noted in only four patients (one each in groups A, C, D, and F). There were no significant differences in the incidence of intraoperative bradycardia (requiring supplemental atropine therapy) or laryngospasm in children who did or did not receive atropine as part of their oral preanesthetic medication regimen.

Finally, there were no significant differences between the various treatment groups with respect to their behavior scores in the PACU or to the need for postoperative opioid analgesic or antiemetic drugs. However, eye opening, response to commands, and discharge from the PACU occurred earlier in the placebo group compared with the group receiving the midazolam-meperidine-atropine combination (Table 2). In analyzing data obtained from midazolam-treated patients (combined groups C and D) undergoing procedures lasting less than 30 min, 30–60 min, and more than 60 min, we found no significant differences among these three subgroups with respect to times to eye opening, response to commands, or discharge from the PACU.

Discussion

Anesthetic inductions in uncooperative children may be associated with arterial oxygen desaturation and postoperative behavioral problems (10). Several studies have reported that preanesthetic medications facilitate separation of children from their parents and improve behavior during induction of anesthesia (1–12). Analogous to a previous study (9), this investigation suggests that oral midazolam is a safe and effective preanesthetic medication. Variable efficacy of oral midazolam may be explained in part by the relatively narrow time frame during which conditions for induction of anesthesia are optimal (i.e., 30–45 min after oral administration).

Our findings may explain why Saarnivarra et al. (13) reported greater anxiolysis with chloral hydrate compared to oral midazolam (0.4–0.6 mg/kg). In that study, patients received the preanesthetic medications 65 ± 12 min before induction of anesthesia. Similarly, Anderson et al. (8) noted that anxiety scores and behavior at induction were no different in children receiving placebo or oral midazolam (0.3 mg/kg) 83 ± 38 min before induction of anesthesia. In contrast, Feld et al. (9) found that oral midazolam (0.5–0.75 mg/kg) administered 30–60 min before induction of anesthesia improved the ease of separation from parents and the quality of mask induction of anesthesia in a dose-related manner. When Molter et al. (14) administered oral midazolam (0.4 mg/kg) approximately 20 min before intravenous induction of anesthesia, they noted a mild or absent sedative effect in 76%–84% of patients, but 67%–88% were cooperative during the insertion of an intravenous catheter before induction of general anesthesia. Similarly, Spahr-Schopfer et al. (15) recently reported that oral midazolam (0.5–1.0 mg/kg) was an effective preanesthetic medication if given 30 min before separation. These data (and data from our current study) suggest that separation from parents and induction of anesthesia should occur 30–45 min after oral administration of midazolam (0.5 mg/kg) to obtain optimal preoperative sedation, ease of separation from parents, and acceptance of the anesthesia face mask.

When oral midazolam was administered alone or in combination with atropine and meperidine, it was found to be safe and effective without altering the cardiovascular or oxygen saturation values in the preoperative or immediate postoperative periods. Furthermore, recovery from anesthesia was not prolonged by oral midazolam preanesthetic medication, even after short surgical procedures lasting less than 30 min. In fact, 53% of the patients in group M (midazolam alone or in combination with atropine) underwent operations lasting 30 min or less. These findings are supported by the recent observations of McMillan and colleagues (16) in children undergoing minor general and dental surgical procedures averaging less than 45 min. As the patients we studied were healthy children, our safety, efficacy, and recovery data cannot be extrapolated to situations involving children with underlying cardiopulmonary diseases or central nervous system disorders.

In this clinical study, the addition of atropine to the oral preanesthetic medication regimen did not

alter sedation, behavior during separation and induction, or the incidence of perioperative complications (e.g., laryngospasm, airway obstruction, and bradycardia). As atropine did not affect perioperative complications, we would recommend that the practice of routinely administering oral atropine preanesthetic medication to all pediatric patients be reexamined, particularly with the decreased use of succinylcholine in this patient population (17–20).

Although patients who received meperidine in our study (groups E and F) were noted to have an increased level of sedation with time, the sedation scores in these two groups did not differ significantly from the other midazolam treatment groups. Of interest, the addition of midazolam to the meperidine-atropine combination did not produce any clinical evidence of respiratory depression in this healthy patient population. Surprisingly, there was no decrease in the PACU opioid requirement (for the treatment of postoperative pain) in patients who did or did not receive oral meperidine preoperatively. Although children given the meperidine-midazolam-atropine combination (group F) had longer discharge times than the other groups, this may have been related to the greater length of their surgical procedures. Thus, we would conclude that the addition of meperidine to the preanesthetic medication regimen did not provide any clinically significant benefits to our study population.

In summary, midazolam (0.5 mg/kg) is a safe and effective preanesthetic medication in healthy children when administered orally 30–45 min before induction of anesthesia. Use of oral midazolam alone or in combination with atropine did not alter recovery times even after surgical procedures lasting less than 30 min.

We thank Drs. Karen Weiss and David Desertspring, and Linda Kratz, RN, for their assistance during this study. In addition, the cooperation of the nursing staff in the outpatient surgery unit at St. Louis Children's Hospital was greatly appreciated.

References

1. White PF. Pharmacologic and clinical aspects of preoperative medication. Anesth Analg 1986;65:963–74.
2. Freeman A, Bachman L. Pediatric anesthesia: an evaluation of preoperative medication. Anesth Analg 1959;38:429–37.
3. Nicolson SC, Betts EK, Jobes DR, et al. Comparison of oral and intramuscular preanesthetic medication for pediatric inpatient surgery. Anesthesiology 1989;71:8–10.
4. De Jong PC, Verburg MP. Comparison of rectal to intramuscular administration of midazolam and atropine for preanesthetic medication of children. Acta Anaesthesiol Scand 1988; 32:485–9.
5. Wilton NCT, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology 1988;69:972–5.
6. Spear RM, Yaster M, Berkowitz ID, et al. Preinduction of anesthesia in children with rectally administered midazolam. Anesthesiology 1991;74:670–4.
7. Brzustowicz RM, Nelson DA, Betts EK, et al. Efficacy of oral premedication for pediatric outpatient surgery. Anesthesiology 1984;60:475–7.
8. Anderson BJ, Exarchos H, Lee K, Brown TCK. Oral premedication in children: a comparison of chloral hydrate, diazepam, alprazolam, midazolam and placebo for day surgery. Anaesth Intensive Care 1990;18:185–93.
9. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric patients. Anesthesiology 1990;73: 831–4.
10. Morgan-Hughes JO, Bangham JA. Pre-induction behavior of children. Anaesthesia 1990;45:427–35.
11. Nelson PS, Streisand JB, Mulder SM, et al. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine for premedication in children. Anesthesiology 1989;70:616–21.
12. Desjardins R, Ansara S, Charest J. Pre-anesthetic medication in paediatric day-care surgery. Can Anaesth Soc J 1981;28:141–8.
13. Saarnivarra L, Lindgren L, Klemola U-M. Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. Br J Anaesth 1988;61:390–6.
14. Molter G, Castor G, Altmayer P, Büch U. Psychosomatic, sedative and hemodynamic reactions following preoperative administration of midazolam in children. Klin Padiatr 1990;202: 328–33.
15. Spahr-Schopfer IA, McMillan C, Sikich N, et al. Safety of oral midazolam premedication for use in children (abstract). Anesthesiology 1991;75(Suppl):A921.
16. McMillan C, Spahr-Schopfer IA, Sikich N, et al. Efficacy and feasibility of oral midazolam premedication in pediatric day surgery (abstract). Anesthesiology 1991;75(Suppl):A27.
17. Sjovall S, Kanto J, Iisalo E, et al. Use of atropine in connection with oral midazolam premedication. Int J Clin Pharmacol Ther Toxicol 1988;22:184–8.
18. Cartabuke RS, Davidson PJ, Warner LO. Is premedication with oral glycopyrrolate as effective as oral atropine in attenuating cardiovascular depression in infants receiving halothane for induction of anesthesia? Anesth Analg 1991;73:271–4.
19. Miller BR, Friesen RH. Oral atropine premedication in infants attenuates cardiovascular depression during halothane anesthesia. Anesth Analg 1988;67:180–5.
20. Mirakhur RK. Premedication with atropine or glycopyrrolate in children. Effects on heart rate, rhythm during induction and maintenance of anaesthesia. Anaesthesia 1982;37:1032–6.

Vasopressor Therapy for Hypotension During Epidural Anesthesia for Cesarean Section: Effects on Maternal and Fetal Flow Velocity Ratios

Peter M. C. Wright, MB, FFARCS, Mohammed Iftikhar, MB, MRCOG, Kieran T. Fitzpatrick, MB, FFARCS, James Moore, MD, FCANAES, and William Thompson, MD, FRCOG

Department of Anesthetics, The Queen's University of Belfast; Department of Obstetrics and Gynaecology, Institute of Clinical Sciences; and Jubilee Maternity Hospital, Belfast, Northern Ireland

The purpose of this study was to identify the influence of hypotension as a result of epidural anesthesia and of its treatment with either ephedrine or methoxamine on uteroplacental and umbilical flow velocity ratios and fetal acid-base status. Fifty healthy women with an uncomplicated full-term pregnancy were studied during elective cesarean section under epidural anesthesia. A method of continuously recording flow velocity waveforms was used that allowed the identification of simultaneous values of maternal and fetal Doppler indices related to events during the induction of anesthesia. In 15 patients in whom arterial blood pressure did not decrease, the uteroplacental pulsatility index (UtPI) did not change, but the umbilical pulsatility index (UmPI) decreased from a mean (95% confidence interval) of 0.98 (0.88–1.09) to 0.91 (0.82–0.99) ($P < 0.05$). In 32 patients who experienced hypotension of at least 15%, the UtPI increased from 0.82 (0.76–0.89) to 1.04 (0.92–1.17) ($P < 0.01$). Treatment with ephedrine had no influence on either the UtPI or UmPI, but treatment with methoxamine resulted in brief increases in the UtPI of 0.47 (0.24–0.69) during the first 5 min after its administration; the increases were brief and resolved within 2 min. The choice of vasopressor drug had no influence on the UtPI recorded just before surgery commenced (final UtPI), but those patients who experienced hypotension had significantly larger final UtPIs (1.02 (0.91–1.10)) than those who never became hypotensive (0.86 (0.72–0.99)), and this was associated with significantly increased placental hydrogen ion gradients. The choice of vasopressor drug appears to be of minor importance compared with the avoidance of hypotension.

(Anesth Analg 1992;75:56–63)

Lumbar epidural anesthesia is extensively used for delivery by cesarean section and is widely accepted as offering advantages over general anesthesia (1). Hypotension may occur during the induction of epidural anesthesia and if severe or prolonged, will compromise fetal well-being (2).

In treating episodes of hypotension, vasopressor therapy is frequently required to obtain an immediate response. Ephedrine, a mixed α- and β-adrenergic agonist, is widely used, and drugs with pure α-adrenergic agonist activity are avoided because animal studies indicate that they reduce uteroplacental blood flow (3). However, the use of pure α-agonists to treat hypotension from epidural anesthesia for cesarean section in humans did not result in fetal acidosis, and their lack of chronotropic activity may make them desirable for use in pregnant women with preexisting cardiac disease (4). In another publication (5), their use is suggested in spinal anesthesia because hypotension occurs more rapidly and can be more severe than with epidural blockade.

Difficulties in the repeated measurement of human uteroplacental absolute blood flow have prevented the evaluation of vasopressor therapy in this respect. However, Doppler velocimetry does enable the repeated semiquantitative evaluation of both uteroplacental and fetoplacental flow resistance. The purpose of this study was to evaluate the effects of both acute hypotension and its treatment with either ephedrine or methoxamine (a pure α_1-adrenergic agonist) on uteroplacental and fetoplacental flow resistance and fetal outcome by using a method that allowed

Accepted for publication February 20, 1992.

Address correspondence to Dr. Wright, Department of Clinical Anaesthesia, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland.

Reprints are not available.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

simultaneous recording of maternal cardiovascular changes and those occurring in the uteroplacental circulation.

Methods

This study was approved by the local medical ethical research committee, and each patient provided informed consent. Fifty healthy women in the age range 18–40 yr undergoing elective cesarean section for cephalopelvic disproportion, breech presentation, or repeat cesarean section were studied. All the women recruited had a full-term uncomplicated singleton gestation.

The patients were given ranitidine 150 mg by mouth on the evening before and the morning of surgery. In the operating room the patients were placed in a 15° left lateral tilt position, and intravenous access was established with a 14-gauge cannula in a large arm vein. With the patient in the left lateral position, an 18-gauge epidural catheter was introduced through a 16-gauge Tuohy needle at the L3-4 interspace, leaving 3 cm of the cannula lying in the epidural space. A 3-mL test dose of 2% lidocaine with epinephrine (5 μg/mL) was administered. The patient was returned to the 15° tilt position, and a rapid intravenous infusion of Hartmann's solution (10 mL/kg) followed. After 5 min, an additional 17 mL of 2% lidocaine with epinephrine was given over a period of 2 min.

Patients in whom hypotension (defined as a reduction in systolic blood pressure of 15% or any reduction to <90 mm Hg) developed during a 20-min period after the completion of the epidural dose received prompt vasopressor therapy. They were randomly allocated to receive either ephedrine (12 mg IV) as a bolus injection and, after 5 min, 12 mg infused in 500 mL of Hartmann's solution over the subsequent 10 min; or methoxamine (2 mg IV), followed by 2 mg as an infusion. These dosage schedules had been determined during a preceding study in nonpregnant patients to represent equipotent pressor doses in the presence of regional anesthesia. Further increments of ephedrine (3 mg) or methoxamine (0.5 mg) were administered as required before delivery to maintain maternal blood pressure above the threshold value. The patients and those investigators responsible for conducting observations were unaware of the treatment, but because of the nature of the therapy being administered there was always an anesthesiologist present who had knowledge of the vasopressor therapy.

Twenty minutes after completion of the epidural injection, the level of the resultant block was assessed with a cold stimulus (ethyl chloride spray). The block was supplemented if necessary and surgery was allowed to proceed.

Measurements

Maternal heart rate and blood pressure were measured during the induction of epidural blockade at 1-min intervals and at 2.5-min intervals during surgery with the Datascope 2200 I. The uteroplacental flow velocity waveform was displayed with a Doptek continuous-wave spectral analyzer; the probe was directed at the uterine artery just superior to the inguinal ligament on the left side. (The left side was chosen rather than the side of placental implantation [6] because, in the left tilt position, this is technically easier and results in a better quality recording.) A second identical continuous-wave analyzer was used to obtain the flow velocity waveform of the umbilical artery. All hemodynamic data were recorded with two industrial-quality digital stereo video recorders; the Doppler-shifted signals obtained from the two circulations under consideration were recorded onto the audio channels of the two recorders. The maternal heart rate and blood pressure were recorded onto the video channel of both recorders with a video camera directed at the datascope monitor. A clock on-screen provided information on timing, and prearranged signals were made to indicate the completion of the epidural injection and the administration of vasopressor drugs. Such a recording arrangement enabled the continuous tracking of the flow velocity profile of each vessel, avoiding the pitfall of moving the probe and replacing it on a different portion of the vessel with a different flow profile (7). It was also possible to analyze the waveforms off-line and obtain truly simultaneous values for uteroplacental and umbilical circulations that could be related to episodes of hypotension and vasopressor therapy.

The time of the epidural injection, any hypotensive episode, the skin and uterine incisions, and the delivery were recorded. At delivery, umbilical artery and venous and maternal arterial blood samples were obtained and analyzed promptly for gas tensions and pH (Corning 168). Apgar scores were assigned by an investigator in a blinded manner at 1 and 5 min, and neonatal resuscitation requirements were recorded. After the operation, maternal pulse and heart rate were measured every 15 min for the first 2 h.

During the subsequent analysis (which was performed with the built-in spectral analyzer and software), Doppler ratios, fetal heart rate, and maternal hemodynamic values were defined just before the epidural injection and at the lowest recorded systolic arterial pressure during the 20 min after the total dose of local anesthetic had been given. If vasopressor treatment was given, recordings were analyzed at

Table 1. Demographic Characteristics of the 32 Patients in the Ephedrine (n = 17) and Methoxamine (n = 15) Groups and the 15 Nonhypotensive Control Subjects

	No hypotension	Hypotension	
		Ephedrine	Methoxamine
Age (yr)	27 (4)	31 (5)	29 (5)
Weight (kg)	77 (14)	80 (11)	75 (11)
Height (cm)	160 (11)	160 (6)	157 (5)
Gestation (wk)	40 (1)	39 (1)	39 (1)
Fetal weight (g)	3407 (435)	3471 (381)	3497 (306)

Data are presented as mean values (SD).

1-min intervals for 5 min after its administration. Values were also defined just before the commencement of surgery.

Unless otherwise stated, data are presented throughout as mean values and 95% confidence intervals or as proportions and frequencies. Hypothesis testing between the ephedrine and methoxamine series was carried out on Apgar scores at 1 and 5 min, maternal artery to umbilical vein pH gradients, the final uteroplacental Doppler ratios before surgery, and the change in the uteroplacental Doppler ratio between baseline and the final value (change in uteroplacental pulsatility index, Δ UtPI). Tests used included Student's t-test and contingency table analysis, as appropriate. Other statistical reporting is subsidiary but includes an analysis of changes associated with an episode of hypotension, a comparison of patients who did or did not display an episode of hypotension, and the effects across time of bolus vasopressor effects using repeated measures analysis of variance and post hoc paired t-tests. Those patients who did not receive vasopressor treatment are referred to as control subjects.

Results

Fifty patients were studied, but three were excluded from this analysis because signs of overt aortocaval syndrome developed before completion of the epidural injection, which prevented adherence to the study program. Of the remaining patients, hypotension, which required treatment with a vasopressor, developed in 32; 17 received ephedrine, and 15 received methoxamine. Where there was conflict between the two Doppler analyzers, the uterine artery was given priority so that umbilical Doppler ratios were obtained in only 34 cases: 12, 13, and 9 in the control, ephedrine, and methoxamine groups, respectively. Demographic characteristics of the groups are shown in Table 1, and cardiovascular characteristics recorded on the day before surgery are shown in Table 2, along with data on induction to delivery and uterine incision to delivery intervals and upper block height. The patients in the ephedrine and methoxamine groups were broadly comparable in all respects, but the control subjects had significantly greater baseline blood pressure than those who required vasopressor treatment.

Table 2. Preoperative Maternal Cardiovascular Characteristics, Block Height, and the Induction to Delivery (I–D) and Uterine Incision to Delivery (U–D) Intervals

	No hypotension (n = 15)	Hypotension	
		Ephedrine (n = 17)	Methoxamine (n = 15)
Systolic blood pressure (mm Hg)	129 (13)[a]	122 (12)	117 (7)
Diastolic blood pressure (mm Hg)	74 (10)[a]	68 (8)	65 (9)
Heart rate (beats/min)	89 (19)	93 (11)	93 (15)
Upper block height[b]	T5 (T2-7)	T4 (T2-9)	T3 (T2-7)
I–D interval (min)	44 (8)	38 (6)	37 (5)
U–D interval (s)	113 (73)	109 (61)	102 (45)

Data are presented as mean values (SD).
[a] $P < 0.05$ compared with the ephedrine and methoxamine series combined.
[b] Median and range.

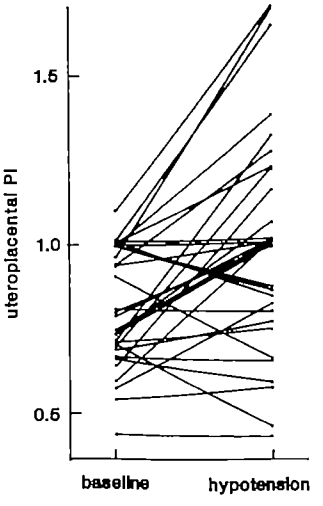


Figure 1. The change in uteroplacental pulsatility index (PI) in those patients who experienced an episode of hypotension, plotted at baseline and at the hypotensive episode.

Effects of Hypotension

The change in uteroplacental and umbilical pulsatility indices from baseline to the lowest recorded blood pressure is plotted in Figures 1 and 2, for each patient who experienced an episode of hypotension, and the changes are summarized along with other hemodynamic data in Table 3 and compared with the values

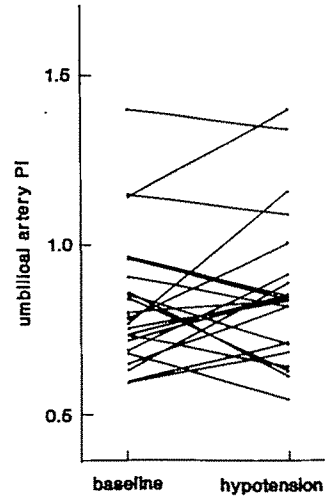


Figure 2. The change in umbilical pulsatility index (PI) in those patients who experienced an episode of hypotension, plotted at baseline and at the hypotensive episode.

of variables recorded during the lowest recorded blood pressure in the control series. Uteroplacental Doppler indices increased during an episode of hypotension ($P < 0.01$) (indicating an increase in flow resistance), whereas umbilical indices remained unchanged. In the control series, uteroplacental Doppler indices remained unchanged throughout the induction of anesthesia, and there was a small but significant reduction in the umbilical indices ($P < 0.05$) after the block became established.

Effects of Vasopressors After Bolus Administration

The effects of the treatment of hypotension with each of the vasopressor drugs on maternal and fetal cardiovascular variables during the 5 min after bolus administration are shown in Figures 3 and 4 and summarized in Table 4. Both ephedrine and methoxamine were effective at increasing systolic and diastolic blood pressure, and differences in the magnitude of the increases at the doses used here were not significant. Ephedrine caused either increases or decreases in maternal heart rate and had little effect on fetal heart rate, whereas methoxamine caused significant decreases in both maternal and fetal heart rate. Ephedrine had no effect on either uteroplacental or umbilical Doppler ratios, but methoxamine caused large but brief increases in uteroplacental ratios, which appeared at 2, 3, or 4 min after administration and lasted for 1 or 2 min at most. Methoxamine had no effect on umbilical Doppler ratios.

Outcome

All of the patients studied had delivery carried out with unsupplemented epidural anesthesia, although one patient in the control series subsequently required general anesthesia because of inadequate sacral lock. Of those patients who required vasopressor therapy, two patients in the ephedrine group and five patients in the methoxamine group required additional increments of vasopressor to maintain blood pressure; the corresponding total doses of ephedrine and methoxamine before delivery were 25.1 mg (95% CI 23.4–26.7) and 4.5 mg (95% CI 4.0–5.0) in the two groups as a whole. Maternal arterial blood pressure was significantly higher in the ephedrine group compared with the methoxamine group at delivery, whereas heart rates were similar in all three groups; systolic arterial pressure was 120 (95% CI 113–127), 111 (95% CI 105–117), and 123 mm Hg (95% CI 114–131) in the ephedrine, methoxamine, and control groups, respectively, and corresponding heart rate values were 98 (95% CI 87–109), 90 (95% CI 81–99), and 103 beats/min (95% CI 90–116). There were no statistically significant differences between the ephedrine and methoxamine groups in the predetermined variables for hypothesis testing (Table 5). The previously identified increases in uteroplacental pulsatility index that occurred during an episode of hypotension and not in the control series persisted and were accompanied by significantly greater placental pH gradients in those who experienced an episode of hypotension compared with the control series (Table 6).

Adverse Effects

The incidence of hypotension <100 mm Hg during this study was 29 of 47 (61%); that <90 mm Hg was 11 of 47 (23%). Nausea was very common (70%) in those in whom hypotension developed and invariably responded to vasopressor treatment. Postoperative hypertension (systolic arterial pressure >150 mm Hg) or hypotension (systolic arterial pressure <90 mm Hg) did not occur during the first 2 h of recovery.

Discussion

Hypotension occurring during lumbar epidural analgesia for cesarean section is detrimental to fetal well-being (8), although it has been suggested (4,9) that brief episodes of reduced arterial blood pressure treated rapidly do not constitute a hazard. At the same time, bolus treatment with vasopressor drugs, particularly pure α-adrenergic agonists, has been demonstrated to reduce uteroplacental blood flow in animals (3). Ephedrine (a mixed α- and β-adrenergic agonist) is widely used, and the few studies in humans that have been reported seem to suggest that α-adrenergic agonists are acceptable in human full-term pregnancy (4,5). This study attempts to measure

Table 3. Mean (95% confidence interval) Changes From Before the Epidural Injection (Baseline) to the Lowest Recorded Systolic Arterial Pressure

	Nonhypotensive control subjects (n = 15)			Hypotensive patients (n = 32)		
	Baseline	Lowest SAP	Change	Baseline	Lowest SAP	Change
Systolic BP (mm Hg)	128 (126 to 136)	122 (113 to 133)	−5.8 (−13 to 1.3)	119 (16 to 123)	90 (86 to 94)	−29.5 (−35 to −24)[a]
Diastolic BP (mm Hg)	74 (68 to 80)	57 (52 to 64)	−16 (−22 to −10)	66 (63 to 70)	45 (42 to 48)	−22 (−26 to −17)
Maternal HR (beats/min)	89 (79 to 100)	102 (92 to 112)	13 (8 to 17)	93 (88 to 98)	97 (89 to 106)	4 (−3 to 12)
Fetal HR (beats/min)	135 (130 to 141)	138 (134 to 142)	4 (−3 to 11)	140 (137 to 144)	141 (137 to 146)	1 (−4 to 6)
Uteroplacental PI	0.87 (0.77 to 0.97)	0.87 (0.78 to 0.95)	0.003 (−0.07 to 0.07)	0.82 (0.76 to 0.89)	1.04 (0.92 to 1.17)	0.22 (0.11 to 0.32)[a]
Umbilical PI	0.98 (0.88 to 1.09)	0.91 (0.82 to 0.99)	−0.08 (−0.13 to −0.02)	0.83 (0.74 to 0.92)	0.87 (0.77 to 97)	0.04 (−0.04 to 0.12)[b]

BP, blood pressure; HR, heart rate; PI, pulsatility index; SAP, systolic arterial pressure.
Numbers in parentheses are 95% confidence intervals.
[a] $P < 0.01$ between the groups.
[b] $P < 0.05$ between the groups.

the short- and long-term effects of both hypotension and treatment with either ephedrine or methoxamine (a pure α-adrenergic agonist). The essential findings are that acute hypotension is associated with increases in uteroplacental Doppler ratios (indicating increased resistance to flow); that such increases persist despite vasopressor treatment and normalization of blood pressure; that patients who require vasopressor therapy demonstrate increased placental pH gradients compared with patients who never became hypotensive; and that methoxamine does result in brief increases in uteroplacental Doppler ratios, but they do not persist and there was no difference between the two vasopressor groups in uteroplacental circulatory parameters or fetal outcome.

Doppler velocimetry has appeared in the past decade, and it attempts to assess, semiquantitatively, downstream impedance to flow. The flow velocity waveform is acquired, and the degree of "pulsatility" is reported. Various indices are used (10), but essentially all relate systolic to diastolic velocity; an increasing ratio implies increasing flow resistance, as a high impedance downstream reduces diastolic flow velocity because of reflection of the pulse wave (11). Neither absolute measures of flow or velocity are possible because the vessel diameter and the angle of incidence of the ultrasound beam to the flow are both unknown. However, it may be assumed that an increased Doppler index, representing increased flow resistance, is undesirable in either of the circulations under consideration here. The technique has been validated both clinically (12) and by computer modeling (13); the pulsatility index correlates closely with arterial flow resistance (14) and shows only a minimal intraindividual variation over periods of up to 1 wk when used to evaluate either the uteroplacental (15,16) or umbilical (15,16) circulation. We used two continuous-wave analyzers, which have the advantage of simplicity and the ability to measure Doppler shifts over a very wide range. They cannot be combined with real-time imaging, and thus a potential pitfall is to sample different vessels, especially when uterine measurements are attempted (7). Continuous-wave Doppler has nevertheless been compared with pulsed Doppler and found to correlate very closely (17–19). We continuously tracked the vessel under consideration so as to provide an additional defense against such an error.

Limited epidural anesthesia provided during labor appears to have no influence on either uteroplacental or umbilical Doppler ratios (20,21), but the effect of anesthesia for cesarean section is less clear. Studies of slowly induced blockade, where maternal blood pressure has remained stable, have found either no change in the uteroplacental Doppler ratios (22–25) or a decrease (26). Similarly, the umbilical ratios appear either to remain unchanged (22,23) or to decrease (24,26), as we observed in the control series. Three studies (27–29) have considered the effects of 2% lidocaine with epinephrine, also used during this study. There were no changes in either uteroplacental or umbilical ratios in 12 patients in whom blood pressure remained stable (27). Another series of relatively few patients (28) considered only the umbilical circulation and failed to demonstrate any consistent changes. A third study (29) using lidocaine with epinephrine found increased uteroplacental Doppler ratios in a proportion of the patients, similar to our observations in those who experienced hypotension, that were associated with decreased ratios in the femoral artery. There were no alterations in the umbilical ratios (29). We have demonstrated that any effects on the uteroplacental circulation are associated

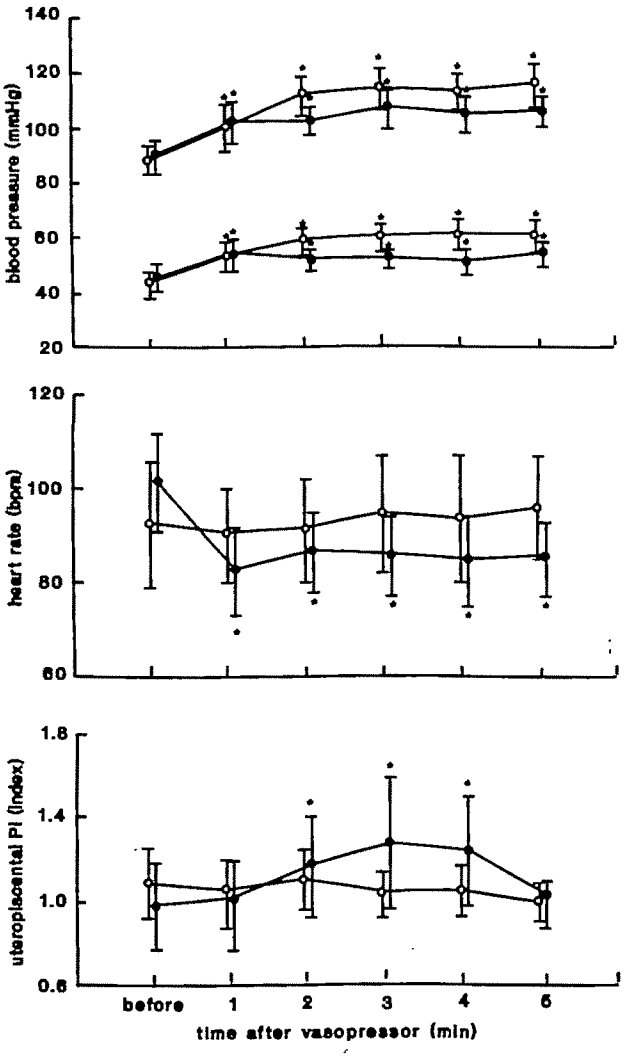


Figure 3. Mean (95% confidence interval) maternal systolic and diastolic blood pressure, heart rate, and uteroplacental pulsatility index (PI) in the 5 min after administration of vasopressor therapy. (●) methoxamine; (○) ephedrine. *$P < 0.05$, compared with baseline. bpm, beats per minute. The increases in PI that occurred in individual patients after methoxamine lasted only 1–2 min but occurred at slightly different times, giving rise to the wide variability seen and an apparently greater duration than that which actually occurred in any individual.

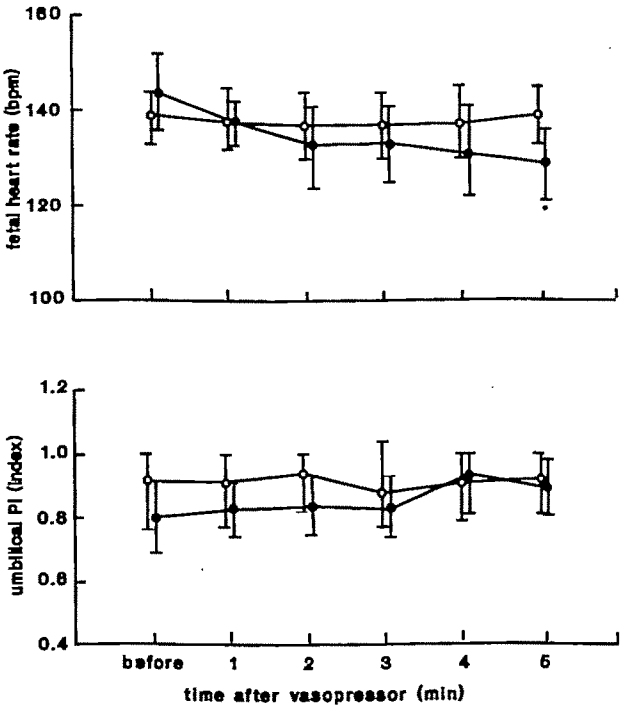


Figure 4. Mean (95% confidence interval) fetal heart rate and umbilical pulsatility index (PI) in the 5 min after administration of vasopressor therapy. (●) methoxamine; (○) ephedrine. *$P < 0.05$, compared with baseline. bpm, beats per minute.

Table 4. Mean (95% confidence interval) Maximal Changes in Cardiovascular Variables and Doppler Ratios in the 5 Minutes After Administration of Vasopressor Therapy

	Ephedrine (n = 17)	Methoxamine (n = 15)
Systolic BP (mm Hg)	33 (24 to 43)	24 (16 to 32)
Diastolic BP (mm Hg)	23 (16 to 30)	13 (8 to 20)
HR (beats/min)	−2.5 (−23 to 18)	−24 (−32 to −16)[a]
Fetal HR (beats/min)	−1.7 (−14 to 10)	−19 (−33 to −5)[a]
Uteroplacental PI	−0.01 (−0.22 to 0.19)	0.47 (0.24 to 0.69)[b]
Umbilical PI	−0.03 (−0.17 to 0.11)	0.12 (−0.04 to 0.28)

BP, blood pressure; HR, heart rate; PI, pulsatility index.
Numbers in parentheses are 95% confidence intervals.
[a] $P < 0.05$ between the groups.
[b] $P < 0.01$ between the groups.

with hypotension rather than epidural anesthesia per se. It is possible that these changes may be associated with mechanisms of defense against hypotension that appear during high epidural blockade (30).

Routine vasopressor therapy during regional anesthesia for cesarean section has recently been recommended (31); however, we used only a limited fluid preload and a low threshold for vasopressor treatment. The indication for vasopressor treatment during this study was a small (15%) reduction in blood pressure. As a result, the 68% of patients who received vasopressor therapy cannot be compared with other reported series. The overall incidence of significant hypotension (systolic blood pressure <90 mm Hg) was 23%, and this is similar to another recent series using lidocaine with epinephrine (32).

Animal studies of the effects of vasopressors on uteroplacental blood flow demonstrate conflicting results. Methoxamine reduced uterine blood flow by 60%, whereas ephedrine had little effect when used to increase blood pressure by 50%, but this was in the absence of regional anesthesia (3). In a study during regional anesthesia but without an intravenous preload, phenylephrine restored maternal blood pres-

Table 5. Comparison of the Predetermined Outcome Variables Between the Ephedrine (n = 17) and Methoxamine (n = 15) Series in Those Patients Who Experienced an Episode of Hypotension

	Ephedrine	Methoxamine
Apgar score 1 min	8 (7–9)	8 (7–9)
Apgar score 5 min	9 (8–10)	9 (9–10)
MA to UV pH gradient	0.08 (0.06–0.1)	0.07 (0.06–0.09)
Final UtPI	1.01 (0.87–1.16)	1.03 (0.86–1.20)
Δ UtPI	0.14 (0.01–0.29)	0.26 (0.1–0.41)

MA, maternal artery; UV, umbilical vein; Ut, uteroplacental; PI, pulsatility index; Δ UtPI, change in the uteroplacental pulsatility index between baseline and the value just before surgery.

Values are mean (95% confidence intervals) or median and range for the Apgar scores.

There are no significant differences.

Table 6. Comparison of the Predetermined Outcome Variables Between the 15 Control Subjects and the 32 Patients Who Experienced Hypotension

	Nonhypotension	Hypotension
Apgar score 1 min	8 (7–9)	8 (7–9)
Apgar score 5 min	9 (9–10)	9 (8–10)
MA to UV pH gradient	0.04 (0.01–0.07)	0.08 (0.07–0.09)[a]
Final UtPI	0.86 (0.72–0.99)	1.02 (0.91–1.10)[b]
Δ UtPI	0.00 (−0.07–0.06)	0.20 (0.09–0.30)[a]

MA, maternal artery; UV, umbilical vein; Ut, uteroplacental; PI, pulsatility index.

Values are mean (95% confidence intervals) or median and range for the Apgar scores.

[a] $P < 0.01$.

[b] $P = 0.055$.

sure without restoring uteroplacental flow (33). Metaraminol (an α-adrenergic agonist) and ephedrine during regional anesthesia both corrected maternal arterial blood pressure and improved uteroplacental blood flow (34,35).

Studies in humans of α-adrenergic agonists are few, but the one formal publication in which phenylephrine was used to treat hypotension after epidural anesthesia failed to demonstrate any deleterious effects (4). The study presented here demonstrates that hypotension, even of a relatively minor degree, is associated with an increase in placental resistance in the uteroplacental circulation. The lasting effect of a brief period of hypotension was noted during a recent investigation (36), and we observed that once an episode of hypotension had occurred, uteroplacental resistance appeared not to return to normal even after correction of the blood pressure. Increased placental pH gradients were detectable at delivery. Methoxamine did increase uteroplacental resistance for a brief period, as predicted by studies in animals; the dose of methoxamine that we used proved to be less potent than the dose of ephedrine in this sample of patients, and a larger dose might have provoked more marked increases in uteroplacental flow resistance. The methodology used here did not allow exact quantification of blood flow, but despite such limitations we cannot recommend the use of methoxamine; however, the choice of vasopressor seems to be a relatively minor consideration compared with the avoidance of hypotension.

References

1. Department of Health and Social Services. Report on confidential enquiries into maternal deaths in England and Wales 1982–84. London: Her Majesty's Stationery Office, 1989.
2. Antoine C, Young BK. Fetal lactic acidosis with epidural anesthesia. Am J Obstet Gynecol 1982;142:55–9.
3. Ralston DH, Shnider SM, DeLorimer AA. Effects of equipotent ephedrine, mephenteramine and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40:354–69.
4. Ramanathan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 1988;32:559–65.
5. Moran DH, Perillo M, Bader AM, Datta S. Phenylephrine in treating maternal hypotension secondary to spinal anesthesia (abstract). Anesthesiology 1989;71:A857.
6. Kofinas AD, Penry M, Greiss FC, Meis PJ, Nelson LH. The effect of placental location on uterine artery flow velocity waveforms. Am J Obstet Gynecol 1988;159:1504–8.
7. Mehalek KE, Rosenburg J, Berkowitz GS, Chitkara U, Berkowitz RL. Umbilical and uterine artery flow velocity waveforms: effect of the sampling site on Doppler ratios. J Ultrasound Med 1989;8:171–6.
8. Brizgys RV, Dailey PA, Shnider SM, Kotelko DM, Levinson G. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987;67:782–6.
9. Vasaka A, Hutchinson HT, Eng M, Allen CR. Spinal and epidural anesthesia: fetal and uterine response to acute hypo and hypertension. Am J Obstet Gynecol 1964;90:800–10.
10. Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio. Br J Obstet Gynaecol 1988;95:581–8.
11. Gosling RG. Extraction of physiological information from spectrum analyzed Doppler ultrasound signals obtained noninvasively from the arterial system. Institute of Electrical Engineers Medical Electronics Monography 1976;21:73–125.
12. Legarth J, Nolsoe C. Doppler blood velocity waveforms and the relation to peripheral resistance in the brachial artery. J Ultrasound Med 1990;9:449–53.
13. Adamson SL, Morrow RJ, Bascom PA, Mo LY, Ritchie JW. Effect of placental resistance, arterial diameter and blood pressure on the uterine arterial velocity waveform: a computer modelling approach. Ultrasound Med Biol 1989;15:437–42.
14. Kinsella SM, Lee A, Spencer JAD. Maternal peripheral arterial resistance changes following lumbar epidural anesthesia for cesarean section: validation of Doppler ultrasound pulsatility index. J Matern Fetal Invest 1991;1:25–8.
15. Pearce JM, Campbell S, Cohen-Overbeek T, Hackett G, Hernandez J, Royston JP. Reference ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulation. Br J Obstet Gynaecol 1988;95:248–56.
16. Hastie SJ, Howie CA, Whittle MJ, Rubin PC. Daily variability of umbilical and lateral uterine wall artery blood velocity waveform measurements. Br J Obstet Gynaecol 1988;95:571–4.
17. Mehalek KE, Berkowitz GS, Chitkara V, Rosenberg J, Berkowitz RL. Comparison of continuous wave and pulsed Doppler

S/D ratios of umbilical and uterine arteries. Obstet Gynecol 1988;72:603–6.
18. Sudmundsson S, Fairlie F, Lingman G, Marsal K. Recording of blood flow velocity waveforms in the uteroplacental and umbilical circulation: reproducibility study and comparison of pulsed and continuous wave Doppler ultrasonography. JCU 1990;18:97–101.
19. Van-Vugt JM, Ruissen CJ, Nienhuis SJ, Hoogland HJ, DeHaan J. Comparison of blood velocity waveform indices recorded by pulsed Doppler and continuous wave Doppler in the umbilical artery. JCU 1988;16:573–6.
20. Patton DE, Lee W, Miller J, Jones M. Maternal, uteroplacental and fetoplacental hemodynamic and Doppler velocimetric changes during epidural anesthesia in normal labour. Obstet Gynecol 1991;77:17–9.
21. Hughes AB, Devoe LD, Wakefield ML, Metheny WP. The effects of epidural anesthesia on the Doppler velocimetry of the umbilical and uterine arteries in normal term labor. Obstet Gynecol 1990;75:809–12.
22. Veille JC, Youngstrom P, Kanaan C, Wilson B. Human umbilical artery flow velocity waveforms before and after regional anesthesia for cesarean section. Obstet Gynecol 1988;72:890–3.
23. Alahuhta S, Rasanen J, Jouppila R, Kangas-Saarela T, Hollmen AI. Uteroplacental and fetal haemodynamics during extradural anaesthesia for caesarean section. Br J Anaesth 1991;66:319–23.
24. Turner GA, Newnham JP, Johnson C, Westmore M. Effects of extradural anaesthesia on umbilical and uteroplacental arterial flow velocity waveforms. Br J Anaesth 1991;67:306–9.
25. Long MG, Price M, Spencer JAD. Uteroplacental perfusion after analgesia for elective caesarean section. Br J Obstet Gynaecol 1988;95:1081–2.
26. Giles WB, Lah FX, Trudinger BJ. The effect of epidural anaesthesia for caesarean section on maternal uterine and fetal umbilical artery flow velocity waveforms. Br J Obstet Gynaecol 1987;94:55–9.
27. Morrow RJ, Rolbin SH, Ritchie JW, Haley S. Epidural anesthesia and blood flow velocity in mother and fetus. Can J Anaesth 1989;36:519–22.
28. Marx GF, Elstein ID, Scuss M, Anyaegbunam A, Fleischer A. Effects of epidural block with lignocaine and lignocaine with adrenaline on umbilical artery velocity wave ratios. Br J Obstet Gynaecol 1990;97:717–20.
29. Baumann H, Alon E, Atanasoff P, Pasch T, Huch A, Huch R. Effect of epidural anesthesia for cesarean delivery on maternal femoral arterial and venous, uteroplacental, and umbilical blood flow velocities and waveforms. Obstet Gynecol 1990;75:194–8.
30. Peters J. Hormonal defense against hypotension and hypoxaemia during high epidural anaesthesia—studies in humans and conscious dogs. Eur J Anaesthesiol 1991;8:317.
31. Anonymous. Epidural block for caesarean section and circulatory changes (Editorial). Lancet 1989;2:1076–8.
32. Norton AC, Davis AG, Spicer RJ. Lignocaine 2% with adrenaline for epidural caesarean section. A comparison with 0.5% bupivacaine. Anaesthesia 1988;43:844–9.
33. Greiss FC, Crandell DL. Therapy for hypotension induced by spinal anesthesia during pregnancy. JAMA 1965;191:89–92.
34. James FM III, Greiss FC, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology 1970;33:25–34.
35. Lucas W, Kirschbaum T, Assali NS. Spinal shock and fetal oxygenation. Am J Obstet Gynecol 1965;93:583–7.
36. Philipson EH, Kuhnert BR, Pimentel R, Amini SB. Transient maternal hypotension following epidural anaesthesia. Anesth Analg 1989;69:604–7.

Combination of Low-Dose Epidural Morphine and Intramuscular Diclofenac Sodium in Postcesarean Analgesia

Hsiao-Lun Sun, MB, Chi-Chen Wu, MB, Min-Shung Lin, MB, Ching-Feng Chang, MB, and Martin S. Mok, MD

Departments of Anesthesiology and Family Medicine, Cathay General Hospital, Taipei, Taiwan, Republic of China and Department of Anesthesiology, University of Southern California, Los Angeles, California

Epidural morphine is used for postcesarean analgesia, and nonsteroidal antiinflammatory drugs are frequently administered to relieve uterine cramps after vaginal delivery. To assess the efficacy of a combination of low-dose epidural morphine and intramuscular diclofenac sodium in postcesarean analgesia, a double-blind, randomized study was conducted. Epidural anesthesia was given to 120 parturients who were randomly allocated into four treatment groups: group A received normal saline solution, 10 mL epidurally and 3 mL intramuscularly (IM); group B received 10 mL of epidural saline solution and 75 mg (3 mL) of diclofenac IM; group C received 2 mg of morphine in 10 mL of epidural saline solution and 3 mL of saline solution IM; and group D received 2 mg of morphine in 10 mL of epidural saline solution and 75 mg of diclofenac IM. Epidural injections were given after delivery of the placenta, and IM injections were given on arrival in the recovery room. Verbal analogue pain scores were recorded at 2, 4, 8, 12, 18, and 24 h after epidural injection. Subjective scores of overall pain relief were also recorded at 24 h. Results showed that scores of overall pain relief were significantly better in group D compared with group A, B, or C ($P < 0.05$). Groups A and B required more supplemental meperidine than groups C and D. None of the subjects in group D requested supplemental analgesia. Compared with the other three groups, group D experienced a better analgesic effect for both wound pain and uterine cramping pain from 4 to 18 h ($P < 0.05$). Incidence of nausea or vomiting, or both, and pruritus occurred more frequently in groups C and D compared with group A or B ($P < 0.05$). No bradypnea was observed during the study period. Diclofenac alone was not effective in postcesarean analgesia. We conclude that combining low-dose (2 mg) epidural morphine and IM diclofenac enhances analgesic efficacy in the treatment of both wound pain and uterine cramps after cesarean section.

(Anesth Analg 1992;75:64–8)

Control of postoperative pain with epidural opioids has become common practice, particularly after cesarean delivery (1–5). A low dose of 2 mg of epidural morphine has been found to be effective in inducing analgesia after lower abdominal surgery (6) but inadequate in a considerable proportion of patients after cesarean section (2,6,7). The difference is noteworthy. Patients after cesarean section suffer from two kinds of acute pain: wound pain and spasmodic uterine contraction pain; however, only a few studies related to postcesarean analgesia have ever addressed this issue (6,8,9). In the past 10 yr, a number of reports (10–14) demonstrating the analgesic efficacy of parenteral nonsteroidal antiinflammatory drugs (NSAIDs) alone or in combination with opioids for various types of acute pain have been presented. The NSAIDs have also been used to relieve uterine cramps after vaginal delivery (8,9,15,16). Therefore, much interest has been generated in finding the means of potentiating the analgesic effect of low-dose epidural morphine without accentuating the adverse effects. In this study, we evaluated the effect of 75 mg of intramuscular (IM) diclofenac sodium, 2 mg of epidural morphine, and the combination of these two regimens in postcesarean analgesia to see whether the combination could be clinically more effective than either drug alone.

Methods

A double-blind, randomized study was approved by the Human Subjects Committee of our hospital and conducted from November 1990 to February 1991. One hundred twenty parturients of ASA physical

This study was conducted at Cathay General Hospital, Taipei, Taiwan, Republic of China.

Accepted for publication March 6, 1992.

Address correspondence to Hsiao-Lun Sun, MB, Department of Anesthesiology, Cathay General Hospital, 280, Section 4, Jen-Ai Road Taipei, Taiwan, Republic of China.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

status I or II about to undergo elective cesarean section were enrolled in the study. Informed consent was obtained from all of them, and a verbal analogue pain score (0, no pain; 10, the worst pain) was explained before induction of anesthesia. After hydration with 750 mL of lactated Ringer's solution, an epidural catheter was inserted through a Portex minipack 16G Tuohy needle at the L2-3 or L3-4 interspace and the tip advanced 3–5 cm cephalad. Sensory anesthesia (determined by pinprick) extending to the T-4 dermatome was achieved with 2% lidocaine with freshly added epinephrine 1:200,000.

After delivery, 10 U of oxytocin and 0.2 mg of ergonovine were administered intravenously. The parturients were allocated at random into one of four treatment groups: group A received 10 mL of epidural and 3 mL of IM normal saline solution; group B received 10 mL of epidural normal saline solution and 75 mg (3 mL) of IM diclofenac; group C received 2 mg of epidural morphine in 10 mL of normal saline solution and 3 mL of IM normal saline solution; and group D received 2 mg of epidural morphine in 10 mL of normal saline solution and 75 mg (3 mL) of IM diclofenac. Epidural injections were given after delivery of the placenta and the IM injections on arrival in the recovery room. Epidural catheters were removed after surgery. All drugs were given in a double-blind manner. After a 2-h stay in the recovery room, patients were sent to the obstetric ward. An Ohmeda Biox 3760 pulse oximeter was used continuously during the study period, and hemoglobin oxygen saturation was recorded every 3 h or at any time it declined to <90%, the alarm setting. Vital signs (blood pressure, heart rate, body temperature, and respiratory rate) were checked every 3 h for 24 h. An anesthesiologist unaware of the treatment groups was responsible for visiting the patients to obtain pain scores at 2, 4, 8, 12, 18, and 24 h after epidural injection. Patients were asked to rate the intensity of wound pain and uterine contraction pain at each interval. Generally, they could differentiate between the two sources of pain without difficulty. At the end of the follow-up, patients were asked to grade the overall pain relief according to the following score: 1, excellent; 2, good; 3, moderate; and 4, poor. Side effects, such as nausea or vomiting, or both, pruritus, and bradypnea (rate < 12 breaths/min) were managed with diphenhydramine (30 mg IM) or naloxone (0.2 mg IV) as necessary. The rescue analgesic was standardized as meperidine 50 mg IM every 4 h at the patient's request. This is the conventional pain management schedule in our obstetric ward. Bleeding was regarded as abnormal when the obstetrician decided to use oxytocin to increase uterine tone.

Parturients with bronchial asthma, severe liver or kidney diseases, peptic ulcer, abnormal bleeding tendency, or known history of allergy to NSAIDs were excluded from the study.

Table 1. Clinical Characteristics of the Four Study Groups

	Group A (n = 29)	Group B (n = 29)	Group C (n = 29)	Group D (n = 30)
Age (yr)	31 ± 1	30 ± 1	31 ± 1	30 ± 1
Weight (kg)	67.4 ± 1.1	69.1 ± 2.0	65.9 ± 1.5	66.5 ± 1.3
Height (cm)	157.3 ± 1.0	157.4 ± 1.0	157.2 ± 0.9	157.2 ± 0.9
Parity (N/M)	10/19	11/18	10/19	13/17

N, nulliparous; M, multiparous.
Values for age, weight, and height are mean values ± SEM; there were no significant differences among the four groups (ANOVA).

Data are expressed as mean values ± SEM. Analyses of variance and the Newman-Keuls test were used to evaluate age, weight, and height of the parturients, pain scores, and scores of overall pain relief, as well as meperidine requirement; χ^2 tests were performed for parity and the occurrence of bleeding, nausea or vomiting, or both, pruritus, and bradypnea. A P value < 0.05 was considered significant.

Results

Within 12 h after cesarean section, large amounts of lochia were observed in three patients, one in each of groups A, B, and C. These three subjects were excluded from the study owing to severe uterine contraction pain after oxytocin infusion. There were no significant differences among the four treatment groups with regard to age, weight, height, and parity (Table 1). There were significant differences among the four groups in terms of both wound pain and uterine contraction pain between 4 and 24 h. Groups C and D had lower wound pain and uterine contraction pain scores than groups A and B after 4 h (Figures 1 and 2). With regard to wound pain, significant differences in pain scores among the four groups at specified times are shown in Figure 1. Although pain scores were generally lower in group B compared with group A, significant differences occurred only during 12–18 h. Compared with group C, wound pain scores were lower in group D, with a significant difference observed at 12 h.

In contrast to the effect of diclofenac on wound pain, scores of uterine contraction pain after the administration of diclofenac in group B were significantly lower than uterine contraction pain scores in group A between 4 and 18 h (Figure 2). Compared with group A or B, both groups C and D had significantly lower scores of uterine contraction pain during most of the 4–18 h. When 2 mg of epidural morphine was used, most of the pain scores re-

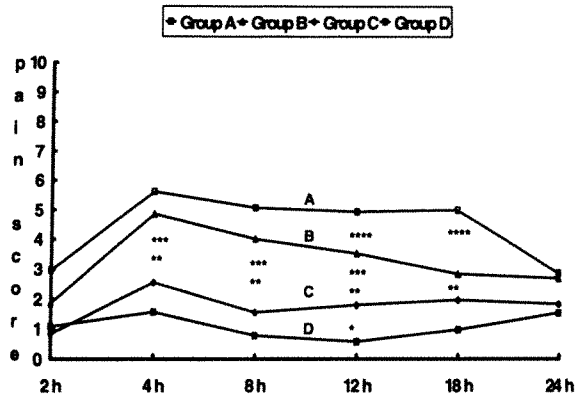


Figure 1. Mean incisional pain scores in the four treatment groups. *$P < 0.05$, group C versus D; **$P < 0.05$, group B versus D; ***$P < 0.05$, group B versus C; ****$P < 0.05$, group A versus B.

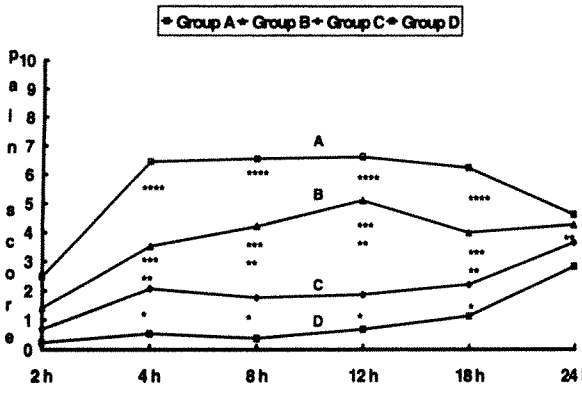


Figure 2. Mean uterine contraction pain scores in the four treatment groups. *$P < 0.05$, group C versus D; **$P < 0.05$, group B versus D; ***$P < 0.05$, group B versus C; ****$P < 0.05$, group A versus B.

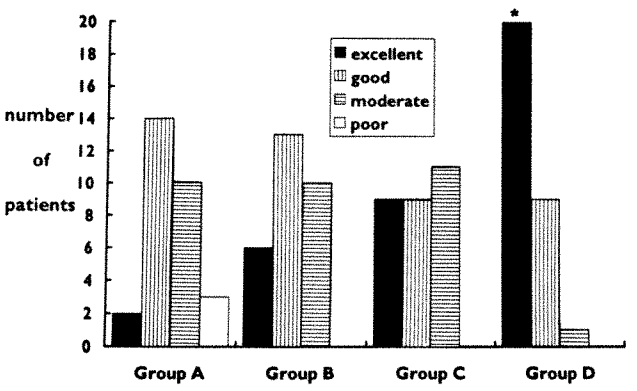


Figure 3. Patient assessment of pain relief in the four treatment groups. *$P < 0.05$, group D versus group A, B, or C.

Table 2. Meperidine Requirement in Each Study Group

	Group A (n = 29)	Group B (n = 29)	Group C (n = 29)	Group D (n = 30)
Total dose (mg)[a]	3650	2450	400	0
Patients requiring treatment (n)	26	20	6	0

[a] $P < 0.05$ among the four groups (ANOVA).

Table 3. Side Effect in Each Study Group

Side effect	Group A (n = 29)	Group B (n = 29)	Group C (n = 29)	Group D (n = 30)
Nausea/vomiting[a]	3	6	10	12
Pruritus[a]	0	1	27	30
Bleeding	1	1	1	0
Bradypnea	0	0	0	0

[a] $P < 0.05$ among the four groups (χ^2-test).

mained low during the first 12 h in both groups C and D and gradually increased thereafter. When a comparison was made between the two groups, a significantly lower score of uterine contraction pain was observed in group D between 4 and 18 h (Figure 2).

In terms of patient satisfaction with pain relief, the overall pain relief score was significantly superior in group D compared with group A, B, or C, with no significant difference among the latter three groups (Figure 3). Approximately 96% of the patients in group D experienced excellent to good pain relief; however, in groups B and C, the efficacy of pain relief decreased to 62%–65%. Groups A and B required more meperidine than groups C and D, whereas no patient in group D requested supplemental analgesia (Table 2).

Incidence of nausea or vomiting, or both, and pruritus occurred more frequently in groups C and D compared with group A or B ($P < 0.05$) (Table 3). The respiratory rate for all subjects remained >12 breaths/min during the study period, and the hemoglobin oxygen saturation was >90% in all patients. Pruritus was the most frequent side effect in the present study, especially in patients who received morphine treatment; however, the condition was mild in most of the patients, and only one patient needed diphenhydramine (30 mg IM) management.

Discussion

We observed higher pain scores and the need for additional analgesia in the 2-mg epidural morphine regimen, compared with the drug combination regimen. This is compatible with previous reports that although 2 mg of epidural morphine is effective for pain relief after lower abdominal surgery, it is not as effective in postcesarean analgesia (2,6,7). The finding that the combination of epidural morphine and IM diclofenac was superior to epidural morphine alone in analgesic quality and duration during the

4–18-h period indicates that diclofenac contributes to additional relief of both wound pain and uterine contraction pain. The efficacy of 2 mg of epidural morphine in postcesarean analgesia was enhanced by the addition of diclofenac. Niv et al. (6) reported spasmodic uterine cramps in a postcesarean section group given 2 mg of epidural morphine. They were subsequently treated with single doses of IM dipyrone. Bloomfield et al. (8,9,15) and Sunshine et al. (16) compared various oral NSAIDs in the treatment of postpartum pain after vaginal delivery and found that NSAIDs were superior to codeine and placebo in relieving uterine cramps. In our study, patients given IM diclofenac consumed less meperidine and had lower pain scores compared with the placebo group. This finding is consistent with other studies (10–12) that indicated that NSAIDs have an opioid-sparing effect. We also observed that diclofenac was more effective in relieving uterine contraction pain than wound pain, indicating the contribution of NSAIDs to the relief of uterine cramps, as shown in other studies (8,9,15,16). Although better than placebo, IM diclofenac alone was not as effective as 2 mg of epidural morphine with regard to relieving both wound pain and uterine contraction pain. The results demonstrated that the 75-mg dose of diclofenac alone was not adequate in postcesarean analgesia.

Prostaglandins have been recognized as important mediators in enhancing postpartum uterine contractile activity (17). Prostaglandins are closely related to dysmenorrhea and are probably the cause of postpartum uterine pain. The NSAIDs were thought to exert their analgesic effect by the inhibition of prostaglandin synthesis, thus reducing both wound pain and uterine contraction pain after cesarean section. In addition to the well-documented peripheral mechanism, a central antinociceptive action of NSAIDs has been demonstrated in both animals (18,19) and humans (20). Diclofenac sodium, a potent prostaglandin synthetase inhibitor, has been shown to possess antiinflammatory, antiedema, antipyretic, and analgesic properties (21,22). Martini et al. (23) also demonstrated increased levels of peripheral β-endorphin after diclofenac treatment and proposed its contribution to analgesia. In the present study, we identified the advantages of each analgesic component ([a] the spinal analgesia of epidural morphine; [b] the peripheral inhibition of prostaglandin synthesis and the nonopioid supraspinal nociceptive reflex inhibition property of NSAIDs) in providing enhanced postcesarean analgesia.

Most of the patients receiving combination analgesia were satisfied with the pain control, and there was no difference among the other three groups with regard to overall pain relief. Our results showed that approximately 96% of the patients receiving the combination of 2 mg of epidural morphine and IM diclofenac experienced excellent to good pain relief. Analgesia resulted from the combination of drugs with different mechanisms, especially the contribution of NSAIDs to uterine cramp pain relief. In view of the high level of effectiveness and average incidence of side effects, postcesarean pain may be relieved by the combination of 2 mg of epidural morphine and IM diclofenac without potentiating other side effects.

The risk of postpartum hemorrhage related to NSAIDs should be taken into consideration. Three patients were found to have abnormal amounts of lochia because of poor uterine contraction; only one of them received diclofenac injection. Diclofenac can prolong bleeding time and reduce platelet aggregation (24,25); however, diclofenac-induced postoperative bleeding is rare in clinical practice (10,24,25). Furthermore, in studies reported by Bloomfield et al. (8,9,15) and Sunshine et al. (16), NSAIDs have been used effectively for relieving postpartum uterine cramps and postepisiotomy pain without significant side effects.

In conclusion, diclofenac sodium alone is not adequate for postcesarean analgesia. Although effective in relieving most wound pain, 2 mg of epidural morphine is not fully effective in relieving uterine contraction pain. The combination of low-dose (2 mg) epidural morphine and 75 mg of IM diclofenac sodium enhances the analgesic effect in the treatment of both wound pain and uterine cramps after cesarean section.

The authors thank Chi-Tse Lee, MPH, Social Medicine Department, National Yang Ming Medical College, for study design consultation and statistical assistance.

References

1. Youngstrom PC, Cowan RI, Sutheimer C, Eastwood DW, Yu JCM. Pain relief and plasma concentrations from epidural and intramuscular morphine in postcesarean patients. Anesthesiology 1982;57:404–9.
2. Rosen MA, Hughes SC, Shnider SM, et al. Epidural morphine for the relief of postoperative pain after cesarean delivery. Anesth Analg 1983;62:666–72.
3. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for postcesarean analgesia—a clinical comparison. Anesthesiology 1988;68:925–9.
4. Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and patient-controlled analgesia for postcesarean section pain relief. Anesthesiology 1988;68:454–7.
5. Douglas MJ, McMorland GH, Janzen JA. Influence of bupivacaine as an adjuvant to epidural morphine for analgesia after cesarean section. Anesth Analg 1988;67:1138–41.
6. Niv D, Rudick V, Chayen MS, David MP. Variations in the

effect of epidural morphine in gynecological and obstetric patients. Acta Obstet Gynecol Scand 1983;62:455–9.
7. Coombs DW, Danielson DR, Pagaue MG, Rippe E. Epidurally administered morphine for postcesarean analgesia. Surg Gynecol Obstet 1982;154:385–8.
8. Bloomfield SS, Cissel GB, Mitchell J, Barden TP. Analgesic sensitivity of two postpartum pain models. Pain 1986;27:171–9.
9. Bloomfield SS, Barden TP, Mitchell J. Naproxen, aspirin and codein in postpartum uterine pain. Clin Pharmacol Ther 1977; 21:414–21.
10. Hodsman NBA, Burns J, Blyth A, Kenny GNC, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 1987;42:1005–8.
11. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine: a study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. Anaesthesia 1987;42:727–31.
12. Carlborg I, Lindoff C, Hellman A. Diclofenac versus pethidine in the treatment of pain after hysterectomy. Eur J Anaesthesiol 1987;4:241–7.
13. Kantor TG. Use of diclofenac in analgesia. Am J Med 1986; 80(Suppl 4b):64–9.
14. Schulze S, Roikjaer O, Hasselstrøm L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. Surgery 1988;103:321–7.
15. Bloomfield SS, Cissel GB, Mitchell J, Barden TP. Codeine and aspirin analgesia in postpartum uterine cramps: qualitative aspects of quantitative assessments. Clin Pharmacol Ther 1983;34:488–95.
16. Sunshine A, Zighelboim I, Olson NZ, Sarrazin CD, Laska E. A comparative oral analgesic study of indoprofen, aspirin, and placebo in postpartum pain. J Clin Pharmacol 1985;25:374–80.
17. Anderson KE, Forman A, Ulmsten U. Pharmacology of labor. Clin Obstet Gynecol 1983;26:56–77.
18. Ferreira SH, Lorenzetti BB, Corrêa FMA. Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 1978;53:39–48.
19. Attal N, Kayser V, Eschalier A, Benoist JM, Guilbaud G. Behavioural and electrophysiological evidence for an analgesic effect of a non-steroidal anti-inflammatory agent, sodium diclofenac. Pain 1988;35:341–8.
20. Willer JC, Broucker TD, Bussel B, Agnès RB, Harrewyn JM. Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind and cross-over study. Pain 1989;38:1–7.
21. Maier R, Manassé R, Riesterer L, Pericin C, Ruegg M, Ziel R. The pharmacology of diclofenac sodium (Voltarol). Rheumatol Rehab 1979;17(Suppl 2):11–21.
22. Todd PA, Sorkin EM. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 1988;35:244–85.
23. Martini A, Bondiolotti GP, Biol D, et al. Diclofenac increases beta-endorphin plasma concentrations. J Int Med Res 1984;12: 92–5.
24. Rorarius M, Miralles J, Bare GA, Palomaki E. Diclofenac versus indomethacin given as intravenous infusions: their effect on haemodynamics and bleeding time and side-effects in healthy subjects. Ann Clin Res 1985;17:306–9.
25. Power I, Chambers WA, Greer IA, Ramage D, Simon E. Platelet function after intramuscular diclofenac. Anaesthesia 1990;45:916–9.

REGIONAL ANESTHESIA AND PAIN MANAGEMENT
Section Editor
Phillip O. Bridenbaugh

Comparison Between Clonidine and Epinephrine Admixture to Lidocaine in Brachial Plexus Block

Dorothee Gaumann, MD, Alain Forster, MD, Marthe Griessen, PhD, Walid Habre, MD, Olivier Poinsot, MD, and Dominique Della Santa, MD

Department of Anesthesiology, Central Laboratory of Clinical Chemistry, and Department of Surgery, University Hospital, Geneva, Switzerland

The admixture of clonidine or epinephrine to lidocaine for brachial plexus block was studied with regard to duration of block, postoperative analgesia, and plasma concentrations of lidocaine. Thirty-three patients of ASA physical status I and II received an admixture of either clonidine (150 μg; $n = 15$) or epinephrine (200 μg; $n = 18$) to 40 mL of 1% lidocaine in a randomized, double-blind fashion. Bone surgery predominated in those patients receiving clonidine and soft-tissue surgery in those receiving epinephrine ($P < 0.05$). Onset and duration of block were not different between the groups. With the admixture of clonidine, fewer patients were completely pain free for >12 h (13.3%) and pain scores (visual analogue scale 0–10) were higher 6 h after the block (median 4; range 0–6) than with epinephrine (61.1%; median 2; range 0–7, respectively; $P < 0.05$). In patients who had received clonidine, peak plasma concentrations of lidocaine were higher (10.29 ± 2.96 μmol/L) and occurred earlier (23.7 ± 9.3 min; mean ± SD) than in those treated with epinephrine (6.9 ± 1.71 μmol/L; 72.5 ± 56.2 min; $P < 0.05$). This indicates the absence of a local vasoconstrictor effect of clonidine and implies a reduced margin of safety with regard to local anesthetic toxicity. Although clonidine does not offer advantages compared with epinephrine, it may be a useful adjunct to local anesthetics in those patients in whom the administration of epinephrine is contraindicated.

(Anesth Analg 1992;75:69–74)

The addition of clonidine to local anesthetics in peripheral nerve block prolongs block duration and postoperative analgesia (1–4). The addition of 150 μg of clonidine to 20 mL of 0.75% lidocaine (1) or to 30 mL of 0.35% bupivacaine (2) in femoral nerve block increased the time of postoperative analgesia by a factor of 3 and 2.6, respectively, compared with the local anesthetic with an admixture of 250 μg of epinephrine. In brachial plexus block, 150 μg of clonidine added to 40 mL of 1% mepivacaine with epinephrine 1:200,000 (3) or to 30 mL of 1.5% lidocaine with epinephrine 1:200,000 (4) significantly prolonged postoperative analgesia by a factor of 2 and 1.4, respectively. The local anesthetic-prolonging effect of clonidine seems to be mediated locally at the peripheral nerve, because subcutaneous or intramuscular injection of clonidine did not increase the duration of the block (3,4). The mechanism of action of clonidine at the level of the peripheral nerve is not known. Clonidine, a selective α_2-receptor agonist (5), might evoke local vasoconstriction by postsynaptic adrenergic receptor activation (6), leading to delayed systemic absorption of the local anesthetic and thus to prolongation of the local anesthetic effect. This action of clonidine would be comparable to that of epinephrine, which is used as a standard adjunct to local anesthetics owing to its vasoconstrictor activity (7).

The present study was conducted to compare the effects of an addition of either clonidine or epinephrine to lidocaine for brachial plexus block, with regard to block duration and postoperative analgesia. Lidocaine plasma concentrations were measured because they reflect local vasoconstrictor effects of the adjuncts.

Methods

Thirty-three patients of ASA physical status I or II, scheduled for elective surgery of the hand or forearm, were included in the study, which was conducted in a randomized, double-blind fashion. The study was approved by the hospital ethics committee, and written, informed consent was obtained from all patients.

Study exclusion criteria included medication interfering with arterial blood pressure regulation, regular

Accepted for publication February 20, 1992.
Address correspondence to Dr. Gaumann, Department of Anesthesiology, University Hospital, 1211 Geneva 4, Switzerland.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

intake of analgesic and psychotropic drugs, peripheral neuropathy, and an incomplete axillary plexus block or a time requirement of >10 min to perform the block. This time limit was arbitrarily chosen to reduce the variability in lidocaine plasma concentrations that would result from large variations in injection times.

The study was originally designed to be conducted with 40 patients, equally divided into two groups, during a period of 6–9 mo. It was terminated after 9 mo, with 34 patients having been examined. All axillary blocks were successfully performed, except in one patient in the clonidine group who was excluded from the study.

Patients did not receive any premedication, and no additional medication was administered intraoperatively. On arrival in the anesthesia induction room, patients were equipped in a standard fashion with a three-lead electrocardiogram, an automatic blood pressure device, and a peripheral venous line. After baseline heart rate, arterial blood pressure, pain score, and sedation score had been recorded, the axillary block was performed with 40 mL of 1% lidocaine hydrochloride in all patients. A 1-mL solution containing either 150 μg of clonidine (Boehringer Ingelheim) (clonidine group, $n = 15$) or 200 μg of epinephrine (epinephrine group, $n = 18$) was added to the lidocaine solution immediately before the axillary block injection.

All axillary blocks were performed with the same technique by an experienced anesthesiologist. The arm was supinated and abducted, and the median, ulnar, radial, and musculocutaneous nerves were located with the help of a nerve stimulator. A current of <0.5 mA was applied, and a 23-gauge Top Pole insulated needle was used. Twelve milliliters of the local anesthetic was injected at each of the following points: median, ulnar, and radial nerves, and 5 mL was injected at the musculocutaneous nerve.

After performance of the nerve block, patients were evaluated every 10 min until complete sensory and motor block had been achieved in the different distribution areas of the nerves. Sensory block was evaluated by the pinprick test on a three-point scale (0, normal sensation; 1, blunted sensation; 2, no perception) and by the temperature test to ether (0, normal; 1, loss of temperature perception). Assessment of motor block was derived from the technique described by Bromage (8) on a three-point scale (0, normal motor function with full flexion and extension of elbow, wrist, and fingers; 1, decreased motor strength with ability to move fingers only; 2, complete motor block with inability to move fingers). After termination of the surgery, evaluation of the nerve block was performed every 30 min until complete recovery had occurred.

Pain intensity was evaluated on a weighted visual analogue scale (VAS), which consisted of a sigmoid line with 10 steps, from 0 (no pain) to 10 (worst pain), showing corresponding facial expressions that ranged from smiling to suffering. The VAS score was recorded at 10-, 20-, 30-, 45-, and 60-min intervals after performance of the axillary block and every 30 min thereafter for up to 8 h after performance of the block. Patients were asked in the morning after surgery about the maximal pain they experienced during the night, and their pain score was reassessed.

Patient sedation was evaluated on a five-point sedation scale (0, wide awake; 1, drowsy; 2, dozing intermittently; 3, mostly asleep; 4, only awake when aroused), and their values were recorded simultaneously with the pain scores.

Blood pressure and heart rate, monitored continuously during the performance of the axillary block and the operation, were recorded postoperatively at the same times as the pain scores.

To measure lidocaine plasma concentrations, blood was withdrawn from the peripheral venous catheter at the following time points: before the axillary lidocaine injection (time 0) and at intervals of 10, 20, 30, 45, 60, 90, 120, 180, 240, 360, and 480 min after termination of the axillary injection. Lidocaine in plasma was detected by a fluorescence polarization immunoassay (Abbott Laboratories), which has a sensitivity of 0.43 μmol/L. Plasma for the measurement of lidocaine concentrations could be used for analysis from 13 patients treated with clonidine and from 16 patients treated with epinephrine. Lidocaine elimination in plasma was assumed to proceed by first-order kinetics (9). The elimination half-life ($T_{1/2}$) was determined from the slope of the semilogarithmic plot of the declining lidocaine plasma concentration against time. The area under the curve was obtained by the trapezoidal rule, and the maximal concentration of lidocaine in plasma was calculated as the mean of the highest and its two surrounding values.

Postoperative pain medication was restricted to mefenamic acid. In the morning after surgery, patients were asked about the amount of mefenamic acid taken and the quality of the axillary block as well as the side effects.

Statistical analysis of continuous data was performed with the unpaired *t*-test. A repeated measures analysis of variance was performed to evaluate changes in mean arterial blood pressure and heart rate within each group, followed, if indicated, by the Scheffé test for homogeneity of variance. Analysis of pain and sedation scores and of pharmacokinetic data were performed by the Mann-Whitney U-test. Discrete patients' characteristics data were treated by the

Table 1. Clinical Characteristics of 33 Patients

	Clonidine group (n = 15)	Epinephrine group (n = 18)
M/F	9/6	16/2
Age (yr)	41 ± 14	38 ± 12
Weight (kg)	73 ± 10	68 ± 10
Height (cm)	172 ± 8	172 ± 8
In-/Outpatients	3/12	6/12
Type of surgery (bone/soft tissue)	12/3[a]	5/13
Osteosynthesis	10	4
Removal of osteosynthetic material	2	2
Tendons and ligaments	3	8
Synovectomy	—	3
Arthroscopy	—	1
Duration of operation (min)	75 ± 18	77 ± 32
Duration of tourniquet (min)	71 ± 21	73 ± 32

Values for age, weight, height, duration of operation, and tourniquet application are expressed as mean values ± SD.
[a] $P < 0.05$.

Table 2. Duration of Axillary Block in 33 Patients

	Clonidine group (n = 15)	Epinephrine group (n = 18)
Complete block (min)		
Sensory (pinprick)	22 ± 7	22 ± 7
Sensory (temperature)	18 ± 6	16 ± 7
Motor	22 ± 7	23 ± 8
First sign of recovery (min)		
Sensory (pinprick)	190 ± 30	201 ± 57
Sensory (temperature)	184 ± 38	201 ± 56
Motor	193 ± 55	200 ± 66
Complete recovery (min)		
Sensory (pinprick)	290 ± 62	303 ± 74
Sensory (temperature)	273 ± 56	302 ± 74
Motor	268 ± 54	276 ± 66

Values are expressed as mean values ± SD.

χ^2-test. In all tests, $P < 0.05$ was considered significant. Continuous data are presented as mean values ± SD, and ordinal data as median and range. Baseline values before nerve block performance are shown in the tables and figures as time point 0.

Results

As summarized in Table 1, the two groups of patients were not different with regard to age, body weight, height, duration of operation and tourniquet application, and distribution ratio between inpatients and outpatients. Bone surgery was mainly performed under axillary block supplemented with clonidine, whereas soft-tissue surgery was more frequent in patients who had received epinephrine ($P < 0.05$). The percentage of women tended to be greater in the clonidine than in the epinephrine group ($P = 0.054$).

Onset and recovery of sensory and motor block were not different between the groups (Table 2). Intraoperative pain, due to tourniquet application, was experienced after 73 and 105 min in two patients who had received clonidine and after 50 and 110 min in two patients treated with epinephrine. In these patients, pain ceased immediately after removal of the tourniquet, and additional treatment for pain was not required.

Maximal pain scores during the postoperative period tended to be higher in patients who had received clonidine (median 6; range 1–9) than in those treated with epinephrine (median 3.75; range 0–8.5; $P < 0.05$). There were more patients completely free of pain (VAS = 0) for >12 h after performance of the axillary block (61.1%) in the epinephrine than in the clonidine group (13.3%). The total amount of mefenamic acid required until the next morning was comparable in the two groups, amounting to 1367 ± 834 mg in patients who had received clonidine and 972 ± 776 mg in those who had received epinephrine.

The pain scores during the study are illustrated in Figure 1. A median VAS value of 0 was observed until 180 min after axillary block performance in patients treated with clonidine and until 210 min in patients treated with epinephrine. Thereafter, VAS values tended to be higher in patients who had received clonidine. The pain score was significantly higher in clonidine-treated (VAS: median 4; range 0–6) compared with epinephrine-treated patients 360 min after axillary injection (VAS: median 2; range 0–7).

Sedation scores during the study are presented in Table 3. Clonidine-treated patients showed a significant degree of sedation between 30 and 90 min after axillary injection (sedation score: median 1; range 0–3) compared with patients treated with epinephrine (sedation score: median 0; range 0–1).

There were no differences in mean arterial blood pressure and heart rate between groups throughout the study (data not shown). The mean arterial blood pressure did not change from baseline values in either group. However, in clonidine-treated patients, a small but significant decrease in heart rate was observed at 60 (66 ± 7 beats/min) and 90 min (65 ± 7 beats/min) after axillary block, compared with baseline (75 ± 10 beats/min; $P < 0.05$), whereas no changes occurred within the epinephrine group.

The curves of the lidocaine plasma concentrations are shown in Figure 2 and corresponding pharmacokinetic data in Table 4. The addition of clonidine or epinephrine to lidocaine led to a significant difference in lidocaine plasma concentrations during the first 90 min after injection. In the presence of epinephrine, the lidocaine plasma concentration curve presented a plateau instead of a peak, as observed for clonidine.

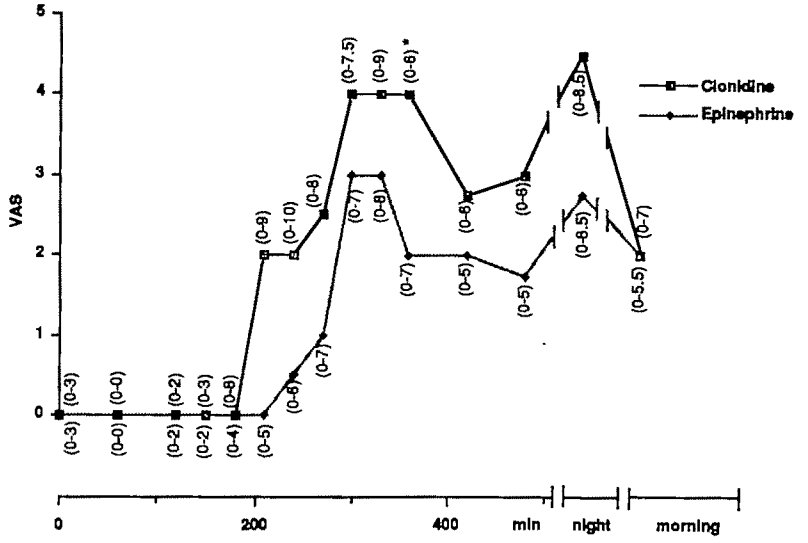


Figure 1. Pain scores (median and range) after axillary block, evaluated on a visual analogue scale (VAS) from 0 (no pain) to 10 (worst pain) in patients who had received an admixture of 150 μg of clonidine (n = 15) or 200 μg of epinephrine (n = 18) to 40 mL of 1% lidocaine for brachial plexus block. *P < 0.05, comparison between groups.

Table 3. Sedation Scores in 33 Patients

Patient group	Time after axillary block (min)											
	0	10	20	30	45	60	90	120	180	240	360	480
Clonidine	0	0	0	1*	1*	1*	1*	1	0	0	0	0
(n = 15)	(0)	(0–2)	(0–3)	(0–3)	(0–3)	(0–3)	(0–3)	(0–2)	(0–2)	(0–4)	(0–2)	(0)
Epinephrine	0	0	0	0	0	0	0	0	0	0	0	0
(n = 18)	(0)	(0–1)	(0–1)	(0–1)	(0–1)	(0–1)	(0–1)	(0–2)	(0–3)	(0–3)	(0–3)	(0–1)

Sedation scores (median and range) were evaluated on a scale of 0–4: 0, awake; 1, drowsy; 2, dozing intermittently; 3, mostly asleep; 4, awake only when aroused.
*P < 0.05.

Maximal plasma concentrations of lidocaine were higher (10.29 ± 2.96 μmol/L) and occurred sooner (23.7 ± 9.3 min) in the clonidine than in the epinephrine group (6.9 ± 1.71 μmol/L; 72.5 ± 56.2 min; P < 0.05). This indicates a more rapid systemic absorption of lidocaine in the presence of clonidine. The elimination half-life of lidocaine in plasma and the area under the curve of lidocaine plasma concentration during the 480 min after axillary injection were not different between the groups. Anesthesia was adequate in all patients, except for two in each group who experienced some discomfort at the end of surgery but did not require any additional medication. Two patients who had received clonidine experienced an episode of nausea and bradycardia in the recovery room at 2 and 4 h after axillary block, with a heart rate between 50 and 55 beats/min; one patient was treated with atropine (0.5 mg IV), whereas bradycardia and nausea ceased spontaneously in the other patient. One patient in the epinephrine group had supraventricular extrasystoles during axillary injection and complained of palpitations. Another patient treated with epinephrine had nausea and bradycardia (50 beats/min) during performance of the block, which ceased spontaneously.

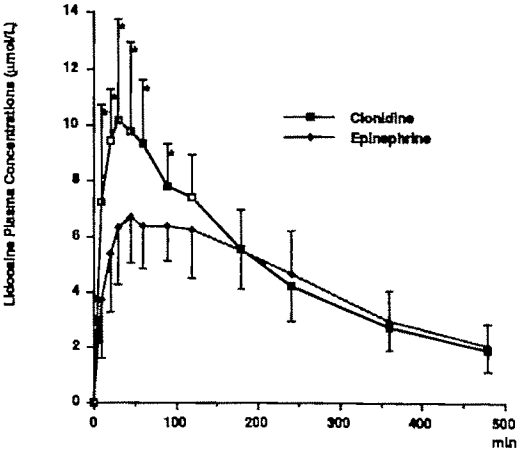


Figure 2. Lidocaine plasma concentrations (mean values ± SD) after axillary block, in patients who had received an admixture of 150 μg of clonidine (n = 13) or 200 μg of epinephrine (n = 16) to 40 mL of 1% lidocaine for brachial plexus block. *P < 0.05, comparison between groups.

Discussion

The short duration of action of plain lidocaine that amounts to approximately 60 min (7) did not allow us

Table 4. Lidocaine Plasma Concentrations in 29 Patients

Patient group	$T_{1/2}$ (min)	AUC (μmol/L × 480 min)	C_{max} (μmol/L)	T_{max} (min)
Clonidine	171.5	2334	10.29	23.70
(n = 13)	±35.8	±507	±2.96	±9.30
Epinephrine	212.5	2116	6.90*	72.50*
(n = 16)	±74.7	±537	±1.71	±56.2

$T_{1/2}$, elimination half-life; AUC, area under the curve; C_{max}, maximal plasma concentration; T_{max}, time of maximal plasma concentration.
Values are expressed as mean values ± SD.
*$P < 0.05$.

to include a control group with plain lidocaine only, which would have provided a better comparison of the effects of clonidine. A longer lasting local anesthetic was not used, because it would have prolonged the period of postoperative surveillance and blood sample collection. The dose of 150 μg of clonidine was chosen on the basis of previous reports (1–4). The dose of epinephrine used (200 μg) resulted in a concentration of 1:200,000, which is considered optimal in providing local vasoconstriction and thus delayed systemic absorption of local anesthetics (7). The results of this study clearly show that the admixture of 150 μg of clonidine or 200 μg of epinephrine to lidocaine provides identical onset, duration, and regression times for axillary plexus blockade. Because epinephrine admixture to lidocaine has been shown to prolong the duration of an axillary plexus block by a factor of approximately 1.4 (10), a similar block-prolonging factor for clonidine can be assumed under the present study conditions.

The mechanism by which clonidine and epinephrine result in a comparable duration of axillary block differs, as evidenced by lidocaine plasma concentrations. In patients who had received the epinephrine admixture, peak plasma concentrations of lidocaine were 33% lower and markedly delayed, compared with patients who had received clonidine. The delayed systemic absorption of lidocaine is mainly due to the vasoconstrictor action of epinephrine (7,10), which is not observed with clonidine. Because a systemic action of clonidine cannot explain the increase in axillary block duration (3,4), clonidine may prolong the effects of local anesthetics by a direct action on the nerve. Recent experiments conducted on the isolated vagal nerve of the rabbit indicate that very low concentrations of clonidine interact in a synergistic fashion with lidocaine to decrease C-fiber action potentials (11).

The addition of epinephrine to local anesthetics for peripheral nerve blocks reduces the risk of local anesthetic toxicity by delaying systemic absorption (7). Because clonidine does not provide local vasoconstriction, the margin of safety with regard to local anesthetic toxicity may be decreased, limiting its use for peripheral nerve block. On the other hand, the admixture of epinephrine to local anesthetics may be contraindicated in patients with severe hypertension, cardiovascular disease, and hyperthyroidism (7), and in these cases, clonidine may present an alternative to epinephrine.

Despite the equal axillary block duration obtained with clonidine or epinephrine admixture, postoperative analgesia was less in patients who had received clonidine. This might be due to the fact that patients and surgical interventions were not perfectly matched as a result of the double-blind study design. Osteosynthetic procedures, which are potentially more painful than soft-tissue operations, were more frequent in patients treated with clonidine than in those who had received epinephrine. Further, the slightly higher percentage of women in the clonidine group might have led to a higher pain rating, as women are more sensitive to painful stimuli than men (12). This imbalance between groups might contribute to the difference between our study and previous reports. These described a significant increase in the duration of postoperative analgesia when 150 μg of clonidine was added to local anesthetics for femoral nerve block (1,2). On the other hand, a certain hyperalgesic effect of clonidine cannot be completely excluded. In experiments in rats, the injection of clonidine into the lateral reticular nucleus, which is involved in the central organization of descending nociceptive modulation, caused a significant increase in thermal nociception (13). Furthermore, there has been a recent report that intrathecal clonidine produced pain in a patient who was given tricyclic antidepressants (14).

Clonidine prevents tourniquet pain if added to a local anesthetic for spinal anesthesia (15). However, in the present study, the incidence of tourniquet pain was not different between the two groups, which suggests that inhibition of tourniquet pain is mainly due to an action at the level of the spinal cord.

Patients who had received clonidine showed significant sedation between 30 and 90 min after axillary injection, indicating the central action of the drug. Sedative effects of clonidine have been extensively documented (16) and are associated with the suppression of central noradrenergic activity (17).

There were no differences in arterial blood pressure and heart rate between the two groups. A small but significant decrease in heart rate from baseline was observed at 60 and 90 min after the axillary injection of clonidine. This slight bradycardic effect, closely corresponding in time to the occurrence of sedation, is the result of adrenergic stimulation of central vagal tone (18).

In conclusion, the admixture of either 150 μg of

clonidine or 200 μg of epinephrine to 40 mL of 1% lidocaine for brachial plexus block provides comparable quality and duration of block. Under the present study conditions, postoperative analgesia was less marked with the clonidine than with the epinephrine admixture. In contrast to epinephrine, clonidine does not cause local vasoconstriction, which implies a reduced margin of safety with regard to local anesthetic toxicity. Although clonidine does not offer advantages compared with epinephrine, it may be a useful adjunct to local anesthetics in those patients for whom the administration of epinephrine is contraindicated.

The authors thank M. W. Griffith, Geneva University Hospital Pharmacy, for preparing and coding the clonidine and epinephrine vials, and Dr. O. Wilder-Smith, Department of Anesthesiology, and J. Weeks for the revision of the manuscript.

References

1. Goldfarb G, Ang ET, Debaene B, Delefosse D, Jolis P. Duration of analgesia after femoral nerve block with lidocaine: effect of clonidine added to the anesthetic solution (abstract). Anesthesiology 1989;71:A644.
2. Goldfarb G, Ang ET, Debaene B, Galet C, Jolis P. Duration of analgesia after femoral nerve block with bupivacaine: effect of clonidine added to the anesthetic solution (abstract). Anesthesiology 1989;71:A643.
3. Singelyn FJ, Gouverneur JM. Duration of block and analgesia after brachial plexus anesthesia with mepivacaine: effect of clonidine added to the anesthetic solution (abstract). Anesthesiology 1990;73:A797.
4. Wyss E, Karp P, Mons P, Bellhacen R, Alame A, Ruelle JL. Effects of intramuscular or local clonidine for prolongation of brachial plexus block with lidocaine (abstract). Anesthesiology 1990;73:A821.
5. Jarrott B, Conway EL, Maccarrone C, Lewis SJ. Clonidine: understanding its disposition, sites and mechanism of action. Clin Exp Pharmacol Physiol 1987;14:471–9.
6. Langer SZ, Duval N, Massingham R. Pharmacologic and therapeutic significance of alpha-adrenoreceptor subtypes. J Cardiovasc Pharmacol 1985;7(Suppl 8):1–8.
7. Scott DB, Cousins MJ. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: JB Lippincott, 1980:86–121.
8. Bromage PR. Mechanism of action. In: Bromage PR, ed. Epidural analgesia. Philadelphia: WB Saunders, 1978:119–59.
9. Rowland M. Drug administration and regimens. In: Melmon KL, Morrelli HF, eds. Clinical pharmacology, basic principles in therapeutics. 2nd ed. New York: Macmillan, 1987:22–70.
10. Kennedy WF Jr, Bonica JJ, Ward RJ, Tolas AG, Martin WE, Grinstein A. Cardiorespiratory effects of epinephrine when used in regional anesthesia. Acta Anaesthesiol Scand 1966; Suppl XXIII:320–33.
11. Gaumann D, Brunet P, Jirounek P, Morel D, Volet B. Effects of clonidine on C-fiber action potential, interaction with lidocaine (abstract). Anesthesiology 1991;75:A656.
12. Feine JS, Bushnell MC, Miron D, Duncan GH. Sex differences in the perception of noxious heat stimulation. Pain 1991;44: 255–62.
13. Ossipov HM, Gebhart GF. Opioid, cholinergic and alpha-adrenergic influences on the modulation of nociception from the lateral reticular nucleus of the rat. Brain Res 1986;384:282–93.
14. Hardy PA, Wells JC. Pain after intrathecal clonidine. An adverse interaction with tricyclic antidepressants? Anaesthesia 1988;43:1026–7.
15. Bonnet F, Diallo A, Saada M, Belon M, Guilbaud M, Boico O. Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 1989;63:93–6.
16. Hossman V, Maling TJB, Hamilton CA, Reid JL, Dollery CT. Sedative and cardiovascular effects of clonidine and nitrazepam. Clin Pharmacol Ther 1980;28:167–76.
17. Drew GM, Gower AJ, Marriot A. Alpha$_2$-adrenoreceptors mediate clonidine-induced sedation in the rat. Br J Pharmacol 1979;67:133–41.
18. Unnerstall JR, Kopajtic TA, Kuhar MJ. Distribution of alpha$_2$-agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res Rev 1984;319:69–101.

Clinical Pharmacokinetics of R(+)- and S(−)-Mepivacaine After High Doses of Racemic Mepivacaine With Epinephrine in the Combined Psoas Compartment/Sciatic Nerve Block

Tom B. Vree, PhD, Erik M. C. Beumer, Aart J. Lagerwerf, Marc A. M. Simon, MD, and Mathieu J. M. Gielen, PhD, MD

Institute of Anesthesiology and Department of Clinical Pharmacy, Academic Hospital Nijmegen Sint Radboud, Nijmegen, and Medisch Spectrum Twente, Enschede, The Netherlands

The purpose of this study was to investigate the pharmacokinetics of R(+)- and S(−)-mepivacaine in 10 male patients after injection of a high dose (731 mg) of racemic R,S-mepivacaine for a combined psoas compartment/sciatic nerve block. Arterial blood samples were taken, and the plasma concentrations of the stereoisomers R(+)- and S(−)-mepivacaine were measured by means of high-performance liquid chromatography (HPLC) with a Chiral AGP column. The S(−) isomer reached higher plasma concentrations than the R(+) isomer. The maximal plasma concentration (C_{max}) of R(+) was 1.54 ± 0.34 μg/mL, whereas that of the S(−) isomer was 2.34 ± 0.51 μg/mL ($P = 0.00050$). The time at which C_{max} was reached (T_{max}) was identical for both isomers. The area under the plasma concentration-time curve from t = 0 to infinity (AUC∞) of S(−)-mepivacaine was almost double that of R(+)-mepivacaine. The elimination half-life ($T_{1/2}$) was identical for both isomers (3 h), which means that the calculated total body clearance and the calculated steady-state volume of the distribution of R(+) are, respectively, 1.7 and 1.5 times larger than that of the S(−) isomer. We conclude that the plasma concentrations of the S(−)-mepivacaine isomer were higher than those of the R(+) isomer because of a smaller volume of distribution and a slower total body clearance.

(Anesth Analg 1992;75:75–80)

Mepivacaine is a racemic mixture of R(+)- and S(−)-mepivacaine, with the S(−) the more active configuration (1,2).

Simon et al. (3) reported good results using a combined psoas compartment block (4) and sciatic nerve block (6) technique with 731 mg of racemic [R(+) + S(−), 50:50]-mepivacaine; however, this dose is larger than the maximal recommended dose for R,S-mepivacaine, which is 500 mg (6). Obviously, recommendation of a single maximal dose should be based on the site of injection (7). The mean maximal plasma concentration of R,S-mepivacaine after a dose of 731 mg was 4.22 ± 1.28 μg/mL, which was reached at 0.99 ± 0.76 h (T_{max}) (5).

The aim of this study was to investigate the pharmacokinetics of R(+)- and S(−)-mepivacaine in 10 patients after injection of 55 mL of racemic mepivacaine 1.33% with epinephrine 1:600,000 for the combined block.

Methods

We studied 10 male patients, ASA physical status I or II (body weight 79.6 ± 13.4 kg, age 40.1 ± 12.5 yr), with no history of allergic reaction to local anesthetics and no coagulation disorders, who were scheduled for orthopedic surgery on one leg. The study was approved by the ethical committee of our hospital, and written, informed consent was obtained from all subjects.

A combination of the psoas compartment block and the sciatic nerve block was used. One hour before surgery, 10 mg of diazepam was administered orally to all patients. Before the nerve blocks were performed, intravenous and arterial (radial) catheters were inserted in all patients. Blood samples for determination of mepivacaine concentrations were collected from the arterial catheter. Routine monitoring for clinical anesthesia was used.

Accepted for publication February 25, 1992.

Address correspondence to Dr. Vree, Department of Clinical Pharmacy, Academic Hospital Nijmegen Sint Radboud, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

To perform the nerve blocks, patients were placed in the lateral position, with the operative limb uppermost (one of the authors performed all nerve blocks). In this position, both the sciatic nerve block (classic approach of Labat [5]) and the psoas compartment block (as described by Chayen et al. [4]) were performed. To locate the sciatic nerve and the lumbar plexus, a 10-cm, 23-gauge needle and a nerve stimulator were used. For the sciatic nerve, 25 mL of R,S-mepivacaine 1.33% (with epinephrine 1:600,000) was injected, and immediately thereafter, the psoas compartment was located and that nerve block was performed with 30 mL of the same solution. The solution for the nerve blocks was prepared by mixing 20 mL of R,S-mepivacaine 2% (with epinephrine 1:200,000) with 40 mL of R,S-mepivacaine 1% (without epinephrine). No sedation was administered.

The first blood sample was taken before injection of the local anesthetic solution. The other blood samples were taken at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after the last injection of R,S-mepivacaine. The time interval between the start of the R,S-mepivacaine injection for the sciatic nerve block and the end of the R,S-mepivacaine injection in the psoas compartment was recorded and was 5 min at maximum. The total dose administered was 731 mg of R,S-mepivacaine [365.5 mg of R(+) and 365.5 mg of S(−)].

The blood samples were stored at 4°C and centrifuged at the end of the sampling procedure. The plasma was then frozen at −18°C and stored until analysis.

Analysis

Reagents and materials. Racemic R,S-mepivacaine HCl (50:50) (Scandicaine, Astra Pharmaceutics, Rijswijk, The Netherlands) was used for the nerve blocks. R,S-mepivacaine HCl and S(−)-ropivacaine were obtained from Astra Pharmaceutics. Solvents were of HPLC grade (Merck, Darmstadt, Germany). A stock solution of 200 mg/L was prepared in 100% methanol. Drug plasma standards were prepared by spiking human blank control plasma with appropriate microliter volumes of the working drug solution. Five plasma standards were obtained with the following concentrations of R,S-mepivacaine: 0.25, 0.50, 1.0, 2.0, and 4.0 μg/mL. Racemic R,S-mepivacaine is stable in solution.

Sample preparation. CALIBRATION CURVE. Twenty microliters of a standard solution of R,S-mepivacaine, 200 μL of blank plasma, 20 μL of internal standard S(−)-ropivacaine (10 or 50 μg/mL in methanol), 0.5 mL of sodium carbonate solution 0.2 M/L, and 1.0 mL of *tert*-butylether were placed in a 2-mL Eppendorf vessel (Eppendorf, Hamburg, Germany), vortexed for 1 min, and centrifuged for 10 min at 3000*g*. From the supernatant, 0.75 mL was transferred to a nipple tube and evaporated with a gentle stream of nitrogen. To the residue, 0.2 mL of the mobile phase was added, and 20 μL was injected onto the HPLC system.

PATIENT SAMPLES. Two hundred microliters of patient plasma, 20 μL of internal standard S(−)-ropivacaine (10 or 50 μg/mL), 0.5 mL of sodium carbonate solution 0.2 M/L, and 1.0 mL of *tert*-butylether were placed in a 2-mL Eppendorf vessel, vortexed for 1 min, and centrifuged for 10 min at 3000*g*.

High performance liquid chromatography. The analysis was performed with a 740 solvent delivery system (Spectra Physics, Eindhoven, The Netherlands), a BD 7 recorder (Kipp Analytica, Delft, The Netherlands), an N 60 injector (Valco H, Chrompack, Middelburg, The Netherlands), a Chiral AGP column (100 cm × 4 mm inside diameter; Chrompack), and a Pye Unicam LC-UV detector (Philips, Eindhoven, The Netherlands). Detection was achieved at 215 nm. The mobile phase consisted of 1 L of a phosphate buffer (0.01 M $Na_2HPO_4 \cdot 2H_2O$ and 0.01 M KH_2PO_4 30:70 vol/vol at pH 6.0) and 60 mL of 2-propanol. The flow rate was 0.88 mL/min. The retention times were 6.8 min for R(+)-mepivacaine, 8.8 min for S(−)-mepivacaine, and 15.2 min for S(−)-ropivacaine.

Validation. The calibration curves were constructed by plotting the peak height ratios R(+), S(−)-mepivacaine/S(−)-ropivacaine against the known concentrations of racemic R,S-mepivacaine ($r > 0.999$). Standard curves were constructed by least-squares regression for calculation of unknown concentrations.

The interday variation is 13.5% for R(+)-mepivacaine and 9.73% for S(−)-mepivacaine (coefficient of variation) at the concentration of 1 μg/mL. These data are, respectively, 10.7% and 11.5% at 5 μg/mL ($n = 16$). The intraday variation is 8.5% for R(+)-mepivacaine and 7.73% for S(−)-mepivacaine (coefficient of variation) at the concentration of 1 μg/mL. These data are, respectively, 6.7% and 7.5% at 5 μg/mL ($n = 10$).

R(+)- and S(−)-mepivacaine were identified according to the ratio in the retention times (capacity factors): R(+)-mepivacaine/R(+)-ropivacaine = S(−)-mepivacaine/S(−)-ropivacaine = 0.58. The internal standard contained 0.5% R(+)-ropivacaine (8). The quantitation limit of R(+)- and S(−)-mepivacaine in plasma was 0.40 μg/mL at a signal-to-noise ratio of 3.

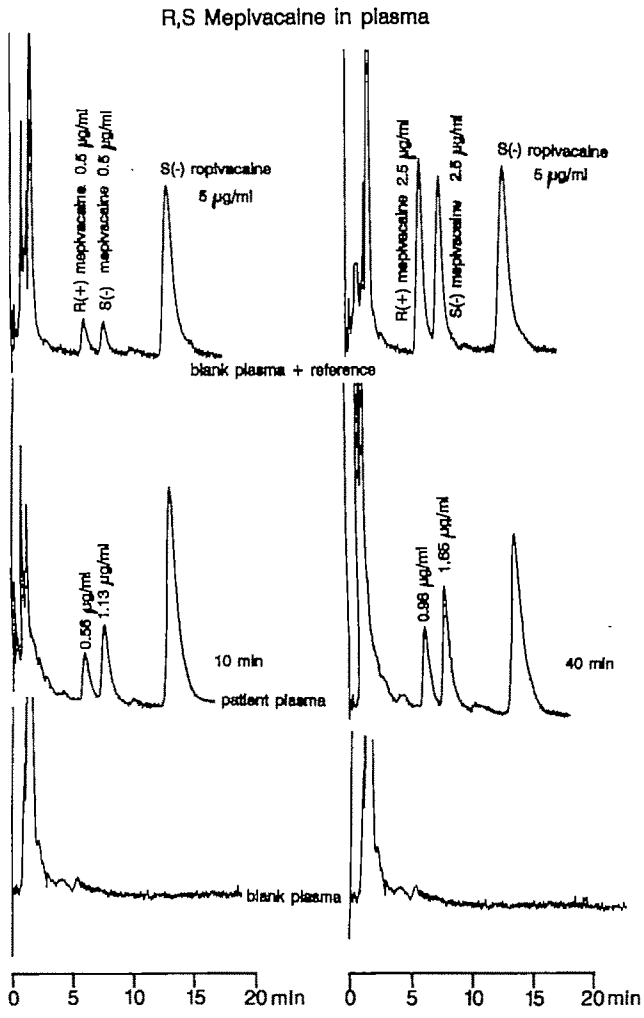


Figure 1. Chromatograms of R(+)- and S(−)-mepivacaine and the internal standard S(−)-ropivacaine in blank plasma spiked with reference compounds (*upper panel*), patient plasma at 10 and 40 min (*middle panel*), and blank plasma (*lower panel*).

Calculations. The plasma pharmacokinetic parameters of R(+)- and S(−)-mepivacaine were calculated as follows: C_{max}, maximal concentration (µg/mL); T_{max}, time of maximal concentration (min); AUC∞, area under the plasma concentration-time curve from t = 0 to infinity (mg·L^{-1}·h); AUMC, area under the plasma moment curve (mg·L^{-1}·h^2); CL, total body clearance (mL/min), dose/AUC; V_{ss}, steady-state distribution volume (L), dose·AUMC·AUC^{-2}. Student's *t*-test was performed according to standard procedures (9).

Results

In all patients, adequate surgical conditions provided by good sensory and motor block were obtained within 10 min, and no additional analgesics were needed. No clinical signs of toxic reactions to the local anesthetic were seen. Figure 1 shows the chromatograms of R(+)- and S(−)-mepivacaine in patient plasma samples. The stereoisomers are well separated from each other and from the internal standard S(−)-ropivacaine.

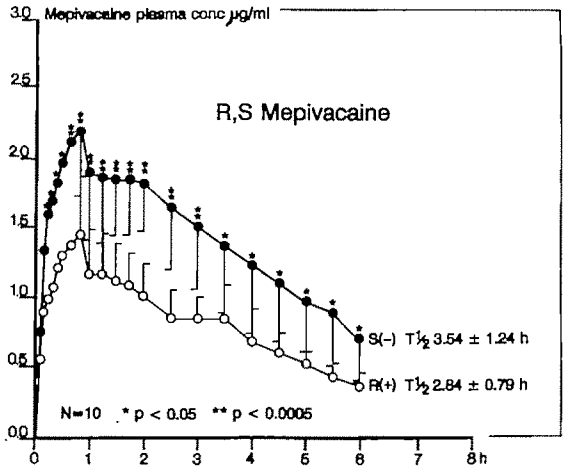


Figure 2. Mean plasma concentration-time curves of R(+)- and S(−)-mepivacaine in 10 patients after administration of 731 mg of R,S-mepivacaine in the psoas compartment. $T_{1/2}$, elimination half-life.

The mean R(+)- and S(−)-mepivacaine plasma concentrations of the 10 patients are shown in Figure 2 and Table 1. The individual pharmacokinetic variables of R(+)- and S(−)-mepivacaine are shown in Table 2 and the mean values of these variables and statistically significant differences in Table 3. Table 3 shows that the S(−) isomer of mepivacaine reaches higher C_{max} plasma concentrations than the R(+) isomer ($P = 0.00050$). The time at which these C_{max} values were reached was similar. The half-life of elimination of both isomers was similar ($P = 0.079$). As a result of these two variables, the AUC∞ of the S(−) isomer is almost twice that of the R(+) isomer ($P = 0.00168$). The lower plasma concentrations of the R(+) isomer resulted in higher calculated values for the total body clearance ($P = 0.00050$) and steady-state volume of distribution ($P = 0.00063$) for the R(+) isomer compared with the S(−) isomer.

Discussion

Much discussion in the literature can be found with regard to toxic effects of local anesthetic drugs during various nerve blocks (5,7,10–15). Large variations in plasma concentrations of mepivacaine have been seen, depending on the site of injection, dosage, age, and physical status. Doses up to 500 mg and blood levels as high as 5–10 µg/mL have been noted without toxic side effects (5,15). This large dose was required with this injection technique to obtain a successful

Table 1. Mean Plasma Concentrations (μg/mL ± SD) of R(+)- and S(−)-Mepivacaine in 10 Patients

Time (h)	R(+)	S(−)	*P* value
0	0	0	
0.083	0.58 ± 0.30	0.76 ± 0.47	0.173
0.167	0.91 ± 0.46	1.34 ± 0.70	0.050
0.250	1.00 ± 0.42	1.60 ± 0.68	0.009
0.330	1.08 ± 0.43	1.72 ± 0.84	0.022
0.417	1.23 ± 0.52	1.82 ± 0.75	0.023
0.500	1.32 ± 0.41	1.98 ± 0.64	0.007
0.667	1.38 ± 0.43	2.13 ± 0.54	<0.0005
0.833	1.46 ± 0.41	2.20 ± 0.46	<0.0005
1.00	1.17 ± 0.32	1.90 ± 0.48	<0.0005
1.25	1.16 ± 0.29	1.86 ± 0.47	<0.0005
1.50	1.12 ± 0.27	1.85 ± 0.40	<0.0005
1.75	1.10 ± 0.23	1.85 ± 0.39	<0.0005
2.00	1.01 ± 0.24	1.82 ± 0.35	<0.0005
2.50	0.85 ± 0.20	1.65 ± 0.45	<0.0005
3.00	0.86 ± 0.16	1.51 ± 0.46	0.002
3.50	0.83 ± 0.25	1.37 ± 0.48	0.006
4.00	0.68 ± 0.24	1.24 ± 0.49	0.010
4.50	0.60 ± 0.13	1.10 ± 0.41	0.009
5.00	0.52 ± 0.08	0.97 ± 0.36	0.015
5.50	0.43 ± 0.09	0.89 ± 0.38	0.009
6.00	0.36 ± 0.10	0.70 ± 0.30	0.070

regional block. The psoas/sciatic administration of mepivacaine resulted in sustained absorption with an apparent half-life of elimination of 3 h (3) instead of 1.5 h after intravenous injection (16). This elimination half-life was also observed after caudal, epidural, and peripheral nerve blocks (15). The relatively slow absorption, followed by distribution and protein binding, limits the toxic action of the protein-free fraction (10–15). Furthermore, the two injections (731 mg) were separated by several minutes, and therefore the danger of acute toxicity was further reduced (6).

The relation between plasma concentration and toxic or pharmacodynamic effects may be valid when the active drug is considered or the combination of active drug and active metabolites. When a racemic mixture is administered, plasma concentrations of the stereoisomers or enantiomers should be measured separately, and the pharmacodynamic effects of each isomer or enantiomer must be investigated.

Stereoisomers should be considered different compounds with different effects. For instance, the S(−) isomer of mepivacaine reaches higher plasma concentrations than the R(+) isomer, and with similar half-lives of elimination of both isomers, the steady-state volume of distribution of the S(−) isomer is much smaller than that of the R(+) isomer ($P = 0.00063$). A similar finding was reported for sheep (17). The similar half-life values of S(−)- and R(+)-mepivacaine indicate that the rate constants of metabolic elimination are similar for both isomers (18,19). The difference in body clearance may be due to differences in metabolic or renal clearance. Therefore, the total

Table 2. Pharmacokinetic Variables of R(+)- and S(−)-Mepivacaine in 10 Patients

R(+)-Mepivacaine (365.5 mg)										
Patient No.	1	2	3	4	5	6	7	8	9	10
Body weight (kg)	70	70	97	61	76	80	80	68	94	100
C_{max} (μg/mL)	1.7	2.0	1.5	1.3	1.4	1.2	0.95	2.0	1.7	1.6
T_{max} (min)	50	40	40	40	40	50	40	30	25	40
AUC∞ ($mg \cdot L^{-1} \cdot h$)	7.52	6.33	4.66	7.43	6.56	6.67	5.30	6.90	6.45	7.85
AUMC ($mg \cdot L^{-1} \cdot h^2$)	34.3	20.1	14.5	38.5	28.8	37.3	28.8	22.2	24.5	35.5
$T_{1/2}$ (h)	2.8	1.8	1.9	3.6	2.8	4.1	3.7	2.3	2.4	3.0
MRT (h)	4.6	3.2	3.1	5.2	4.4	5.6	5.4	3.2	3.8	4.5
V_{ss} (L)	222	184	244	255	245	306	376	171	216	211
CL (mL/min)	811	964	1308	820	930	914	1152	885	946	777
S(−)-Mepivacaine (365.5 mg)										
Patient No.	1	2	3	4	5	6	7	8	9	10
Body weight (kg)	70	70	97	61	76	80	80	68	94	100
C_{max} (μg/mL)	3.0	2.2	1.9	2.6	2.1	2.0	1.6	3.2	2.6	2.2
T_{max} (min)	50	50	40	50	50	50	50	20	25	50
AUC∞ ($mg \cdot L^{-1} \cdot h$)	12.8	7.50	6.73	21.7	11.1	11.8	9.25	12.0	15.6	18.5
AUCM ($mg \cdot L^{-1} \cdot h^2$)	58.6	25.8	22.5	188.8	58.5	69.2	43.5	42.3	85.8	134.7
$T_{1/2}$ (h)	3.0	2.3	2.0	6.2	3.4	4.3	3.6	2.4	3.7	4.5
MRT (h)	4.6	3.4	3.4	8.7	5.3	5.8	4.7	3.5	5.5	7.3
V_{ss} (L)	130	168	182	147	173	181	186	107	130	144
CL (mL/min)	475	813	907	281	547	516	660	507	392	330

C_{max}, maximal concentration; T_{max}, time of maximal concentration; AUC∞, area under the plasma concentration-time curve from t = 0 to infinity; AUMC, area under the plasma moment curve; $T_{1/2}$, half-life; MRT, mean residence time (AUMC/AUC); CL, total body clearance (dose/AUC); V_{ss}, steady-state distribution volume (dose·AUMC·AUC^{-2}).

Table 3. Mean Values (±SD) of Some Pharmacokinetic Variables of R(+)- and S(−)-Mepivacaine in 10 Patients

	R(+) (365.5 mg)	S(−) (365.5 mg)	*P* Value
C_{max} (μg/mL)	1.54 ± 0.34	2.34 ± 0.51	0.00050
T_{max} (min)	39.5 ± 7.62	43.5 ± 11.5	0.18740
AUC∞ (mg·L^{-1}·h)	6.57 ± 0.99	12.71 ± 4.72	0.00168
AUMC (mg·L^{-1}·h^2)	28.4 ± 8.04	73.0 ± 52.1	0.01231
$T_{1/2}$ (h)	2.84 ± 0.79	3.54 ± 1.24	0.07935
MRT (h)	4.30 ± 0.94	5.22 ± 1.74	0.08461
V_{ss} (L)	242.8 ± 60.3	154.8 ± 27.2	0.00063
CL (mL/min)	950.6 ± 163.7	542.8 ± 200.7	0.00050
Body weight (kg)	79.6 ± 13.4	79.6 ± 13.4	1.00000

C_{max}, maximal concentration; T_{max}, time of maximal concentration; AUC∞, area under the plasma concentration-time curve from t = 0 to infinity; AUMC, area under the plasma moment curve; $T_{1/2}$, half-life; MRT, mean residence time (AUMC/AUC); CL, total body clearance (dose/AUC); V_{ss}, steady-state distribution volume (dose·AUMC·AUC^{-2}).

mass balance of each isomer must be determined in order to clarify the nature of the differences in steady-state distribution volume and total clearance of both isomers. The time-course of the surgery and recovery room enabled sampling of two half-life times. For calculation of the exact pharmacokinetic variables, this sampling time is short; therefore the values presented in Table 2 may be regarded as close approximations. At the end of the sampling time, the limit of detection of the HPLC analysis was nearly reached, so a longer sampling time will not give better values of the pharmacokinetic variables.

S(−)-prilocaine (20), S(−)-mepivacaine (2), and R(−)-bupivacaine (2) all act longer than their isomers, despite equal in vitro potency (21). R(−)-bupivacaine has a longer analgesic effect than its S(+) isomer after intradermal injection of both isomers of bupivacaine (21). These effects can be explained by the observed differences in steady-state distribution volume and the higher plasma concentrations of the active isomer. The S(+) isomer of bupivacaine shows higher plasma concentrations than the R(−) isomer, whereas both plasma concentration-time curves run parallel after intrapleural administration of the racemate (22). Both isomers of bupivacaine had concentration-dependent vasodilator and vasoconstrictor effects. Similar behavior might be expected for mepivacaine isomers. A dual effect on smooth muscle has often been observed. Low concentrations of R(+)-mepivacaine increased tension in the rat portal vein, whereas S(−)-mepivacaine had a relaxing effect. Higher concentrations of both isomers relax the portal vein but with S(−)-mepivacaine as the most active isomer (23). Local anesthetics may relax contracted blood vessels in the dog but contract relaxed smooth muscles (24). S(−)-mepivacaine increased the tension of the smooth muscles more than the R(+) isomer at higher concentrations. In contrast, at low concentrations, the R(+) isomer produced more relaxation of smooth muscles (25). Ideally, pharmacodynamic effects of the local anesthetic drugs must be investigated with the optical isomers, as was done for S(−)-ropivacaine by Katz et al. (26) and Rutten et al. (27). S(−)-ropivacaine is the correct form of local anesthetic drug.

In conclusion, in humans the S(−) isomer of mepivacaine reached higher plasma concentrations than the R(+) isomer, which must be the result of a smaller volume of distribution and a slower total body clearance.

References

1. Luduena FP. Duration of local anesthesia. Ann Rev Pharmacol 1969;9:503–20.
2. Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. Arch Int Pharmacodyn Ther 1972;200: 359–69.
3. Simon MAM, Gielen MJM, Lagerwerf AJ, Vree TB. Plasma concentrations after high doses of mepivacaine with epinephrine in the combined psoas compartment/sciatic nerve block. Reg Anaesth 1990;15:256–60.
4. Chayen D, Nathan H, Chayen M. The psoas compartment block. Anesthesiology 1976;45:95–9.
5. Bridenbaugh PO. The lower extremity: somatic blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: JB Lippincott, 1988:424–6.
6. Scott DB. Techniques of regional anesthesia. Fribourg, Switzerland: Mediglobe SA, 1989:122.
7. Scott DB. Maximum recommended doses of local anaesthetic drugs (editorial). Br J Anaesth 1989;63:373–4.
8. Fyhr P, Högström C. A preformulation study on the kinetics of the racemization of ropivacaine hydrochloride. Acta Pharm Suec 1988;25:121–32.
9. Anonymous. SAS user's guide. Basics 1982 edition. Cary, N.C.: SAS Institute Inc., 1982.
10. Jorfeldt L, Löfström B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 1968;12:153–69.
11. Morishima H, Daniel SS, Finster H, et al. Transmission of mepivacaine during continuous epidural anesthesia. Anesthesiology 1966;27:147–54.
12. Moore DC, Bridenbaugh L, Bagdi PA, Bridenbaugh PO. Accumulation of mepivacaine hydrochloride during caudal block. Anesthesiology 1968;29:585–8.
13. Taeger L, Wagner F. Kombinierter ischiadikus/3-in 1 block. Mepivacain HCl 1% versus CO_2-mepivacain 1%. Reg Anaesth 1988;11:50–3.
14. Takasaki M, Oh-oka T, Doi K, Kosaka Y. Blood levels of mepivacaine during continuous epidural anesthesia. Anesth Analg 1987;66:337–40.
15. Tucker GT, Moore DC, Bridenbaugh PO, Bridenbaugh LD, Thompson GE. Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology 1972; 37:277–87.
16. Arthur GR, Scott DHT, Boyes RN, Scott DB. Pharmacokinetic and clinical pharmacological studies with mepivacaine and prilocaine. Br J Anaesth 1979;51:481–5.
17. Mater LE. Disposition of mepivacaine and bupivacaine enantiomers in sheep. Br J Anaesth 1991;67:239–46.
18. Meffin P, Robertson AV, Thomas J, Winkler J. Neutral metabolites of mepivacaine in humans. Xenobiotica 1973;3:191–6.
19. Meffin PJ, Thomas J. The relative rates of formation of the

phenolic metabolites of mepivacaine in man. Xenobiotica 1973; 3:625–32.
20. Akerman B, Persson H, Tegner C. Local anaesthetic properties of the optically active isomers of prilocaine (Citanest). Acta Pharmacol Toxicol 1967;25:233–41.
21. Aps C, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. Br J Clin Pharmacol 1978;6:63–8.
22. Lee EJD, Ang SB, Lee TL. Stereoselective high-performance liquid chromatographic assay for bupivacaine enantiomers. J Chromatogr Biomed Appl 1987;420:203–6.
23. Åberg G, Anderson R. Studies on mechanical actions of mepivacaine (Carbocaine) and its optically active isomers on isolated smooth muscle: role of Ca^{++} and cyclic AMP. Acta Pharmacol Toxicol 1972;31:321–36.
24. Åberg G, Dhuner KG. Effects of mepivacaine (Carbocaine) on femoral blood flow in the dog. Acta Pharmacol Toxicol 1972; 30:267–72.
25. Åberg G, Wahlstrom B. Vascular effects of mepivacaine. Acta Physiol Scand 1969;330(Suppl):71.
26. Katz JA, Bridenbaugh PO, Knarr DC, Helton SH, Denson DD. Pharmacodynamics and pharmacokinetics of epidural ropivacaine in humans. Anesth Analg 1990;70:16–21.
27. Rutten AJ, Mather LE, Nancarrow C, Sloan PA, McLean CF. Cardiovascular effects and regional clearances of intravenous ropivacaine in sheep. Anesth Analg 1990;70:577–82.

Antinociceptive Effects of Phenobarbital in "Tail-Flick" Test and Deafferentation Pain

José M. González-Darder, PhD, Antonio Ortega-Alvaro, MD, Ignacio Ruz-Franzi, MD, and Dolores Segura-Pastor, MD

Departments of Neurosurgery and Anesthesiology, Faculty of Medicine, University of Càdiz, Càdiz, Spain

Deafferentation pain has been related to abnormal electrical hyperactivity in the neurons of the sensory relays in the central nervous system. This electrical activity resembles the epileptoid pattern observed in experimental epileptoid foci. With the aim of preventing this hyperactivity, rats were given long-term treatment with phenobarbital after sciatic transection and dorsal cervical rhizotomy. Daily intramuscular injections of saline solution or 5 and 10 mg/kg of phenobarbital were administered for 20 days, starting 10 days before surgery. Larger doses of phenobarbital delayed the onset and reduced the severity of autotomy. In a test of acute pain, the effect of intraperitoneal (1–16 mg) and intrathecal (100–500 μg) phenobarbital was studied by measuring the "tail-flick" response latency. Intraperitoneal phenobarbital did not modify acute pain, but 500 μg of intrathecal phenobarbital increased the threshold of pain. These results indicate that (a) phenobarbital, a drug with anticonvulsant activity, reduces deafferentation behavior in rats, and (b) intrathecal phenobarbital has an antinociceptive action in acute experimental pain.

(Anesth Analg 1992;75:81–6)

There is a relation between the clinical characteristics of deafferentation pain experienced after injury and painful sensations felt by the patient before deafferentation (1,2). This fact has been explained by hypothesizing that chronic pain produces changes in the central nervous system (3); however, little is known about the pathophysiologic basis of this phenomenon. Sensory neurons are normally under the inhibitory action of the sensory and descending pathways. After deafferentation procedures in animals, such as dorsal rhizotomy or section of peripheral nerves, the surgery is followed by the development of spontaneous hyperactivity of spinal cord dorsal horn neurons (4–7) and other somatosensory nuclei. Similar electrical hyperactivity in patients suffering chronic benign pain in neurons located in the spinal cord was recorded perioperatively by Loeser et al. (8) and, more recently, by Hirayama et al. (9) and Rinaldi et al. (10) in the thalamus of patients with deafferentation pain. Such hyperactivity may be one of the mechanisms involved in the cause of deafferentation pain.

This work was supported by a grant from the CAICYT, Ministerio de Educación y Ciencia, Spain.

Accepted for publication February 28, 1992.

Address correspondence to Dr. González-Darder, Department of Neurosurgery, Faculty of Medicine, University of Cádiz, 11002 Cádiz, Spain.

A few clinical studies report methods for preventing the development of deafferentation pain. Recently, Bach et al. (11) showed that preoperative lumbar epidural blockade with bupivacaine and morphine reduces the incidence of phantom limb pain after amputation. In an experimental study in the model of sciatic section in rats, we showed that autotomy behavior is reduced when the nerve is blocked with bupivacaine before section (12) and a local surgical procedure, such as a centrocentral anastomosis, is performed on the central stump (13).

We designed an experiment aimed at studying the effect of phenobarbital on the prevention of the autotomy behavior that follows deafferentation procedures in rats. Autotomy is now considered to be a response to pain or dysesthesia, and its intensity related to the degree of those abnormal sensations. Blumenkopf and Lipman (14) showed that autotomy is not related to limb anesthesia. Autotomy has also been modified through the use of many surgical and pharmacologic treatments (12,13,15). Phenobarbital is a drug with anticonvulsant activity that can be administered by any route, including intrathecally (16). The rationale for this therapeutic approach is that phenobarbital might reduce the spontaneous activity of deafferented hyperactive neurons and, subsequently, the autotomy behavior. We also tested the effect of phenobarbital in a nociceptive test of acute

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

pain to determine whether phenobarbital had any direct antinociceptive effect.

Methods

Animals and Anesthesia

Adult male Wistar rats, weighing 200–225 g, were used in the studies. For surgical procedures, the animals were intraperitoneally anesthetized with a mixture of ketamine (60 mg/kg) and diazepam (6 mg/kg). The study was conducted in accordance with the guidelines of the Ethics Committee of the International Association for the Study of Pain and was approved by the Research Laboratory of the Faculty of Medicine of Càdiz.

Deafferentation Models of Pain

Animals were randomly assigned to one of two experimental models of deafferentation pain. In the first group, the left sciatic nerve was sectioned cleanly at the midthigh level. Approximately 5 mm of the proximal stump of the nerve was removed to prevent its spontaneous regeneration into the distal nerve stump. In a second group of animals, a cervical posterior rhizotomy was performed by sectioning the C-4 to T-1 dorsal roots. The roots were sectioned on the left side with microsurgical techniques. Animals were given long-term treatment with intramuscular phenobarbital. Rats received daily injections of 5 or 10 mg/kg of phenobarbital for 20 days, starting 10 days before deafferentation. Control animals received saline solution.

In the sciatic section group, 12 and 15 rats were treated with phenobarbital (5 and 10 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively), and 7 control rats received saline solution. In the cervical dorsal rhizotomy group, 13 and 16 rats were treated with phenobarbital (5 and 10 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively), and 8 control rats received saline solution. After surgery, the wounds were closed in layers. No other drugs were administered, and the animals were observed for 4 wk. Each rat was lodged individually in a cage under standard colony conditions. Animals were checked daily to score the autotomy behavior. The following autotomy scale was used: 1 point for the chewing off of one or more nails and an additional point for the removal of each half-toe or metatarsus/carpus and tarsus/carpus (maximum 13 points in upper limb and 7 points in lower limb, due to cutaneous innervation of sciatic nerve).

Acute Antinociceptive Test: "Tail-Flick" Response

A different group of rats underwent long-term implantation of a lumbar intrathecal catheter with an original technique (17). For this purpose, a small microsurgical lumbar laminectomy was performed and the dura mater opened with the tip of a needle. Through this slit, a polyvinyl catheter (0.64 outside diameter; 0.28 inside diameter) was carefully introduced and advanced caudally 1.5 cm. The catheter was firmly secured to paraspinal muscles, tunneled subcutaneously, and pulled out atop the calvarium. The catheter tip was sealed by heat. These animals were studied 4 days later in an short-term algesiometer test. For this test, the tail of the animal was placed under a focused radiant infrared source (Hugo Basile, Milan, Italy) (100-W bulb) to measure the "tail-flick" latency. A humane cutoff time of 10 s was preset to avoid burning. In control animals, 50 μL of saline solution was injected intrathecally through the catheter; in experimental animals, the same volume containing 100, 200, or 500 μg of phenobarbital was delivered. The test was done before injection and 10, 20, and 30 min later. Three measurements were performed at each time on three different points on the tail, and the mean value was considered the latency. The same algesiometer test was also performed in nonimplanted rats receiving saline solution or phenobarbital intraperitoneally. In these experiments, the injected volume was 1 mL, containing 1, 2, 4, 8, or 16 mg of phenobarbital.

The following groups were formed in which tail-flick latency was studied: intraperitoneal saline solution (6 rats) and 1–16 mg of phenobarbital (5–10 rats each group); intrathecal saline (6 rats) and 100, 200, and 500 μg of phenobarbital (5–8 rats each group).

At the end of each experiment, the animals were killed and the spinal column was removed in each case. Specimens from the surgical levels were processed for routine pathological study.

Statistical Analysis

Statistical analysis was done using the χ^2 test and a nonparametric test for comparison of means of paired (Wilcoxon test) and nonpaired (Mann-Whitney test) data. Statistical differences of $P \leq 0.05$ were considered to be significant. Results are expressed as mean values ± SEM. Latency times in the tail-flick test are expressed in the figures as a percentage of the baseline values obtained before phenobarbital injections.

Results

Autotomy Behavior

Table 1 shows the day of onset of autotomy and the percentage of animals developing autotomy after sciatic section. Although there is a delay in the mean day of onset of autotomy in both groups of animals

Table 1. Day of Onset of Autotomy and Percentage of Animals Developing Autotomy (≥1) and Severe Autonomy (≥5)

Group	Day of onset	Autotomy ≥1				Severe autotomy ≥5			
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4
Sciatic section									
Saline solution (n = 7)	3.3 ± 1.1	86	100	100	100	0	15	15	15
PB-5 (n = 12)	6.7 ± 1.4	75	100	100	100	0	0	25	25
PB-10 (n = 15)	7.2 ± 3.5[a]	60	60	60	73	0	0	13	26
Dorsal rhizotomy									
Saline solution (n = 8)	2.8 ± 0.9	87	87	87	87	0	0	12	37
PB-5 (n = 13)	4.7 ± 1.1	85	85	85	85	15	15	23	23
PB-10 (n = 16)	11.8 ± 2.5[b]	44	50	75	75	0	0	0	0

PB-5, phenobarbital (5 mg·kg^{-1}·day^{-1}); PB-10, phenobarbital (10 mg·kg^{-1}·day^{-1}); wk, week.
Onset of autotomy expressed in days ± SEM.
[a] $P < 0.05$, Mann-Whitney test versus saline solution.
[b] $P < 0.01$, Mann-Whitney test versus saline solution.

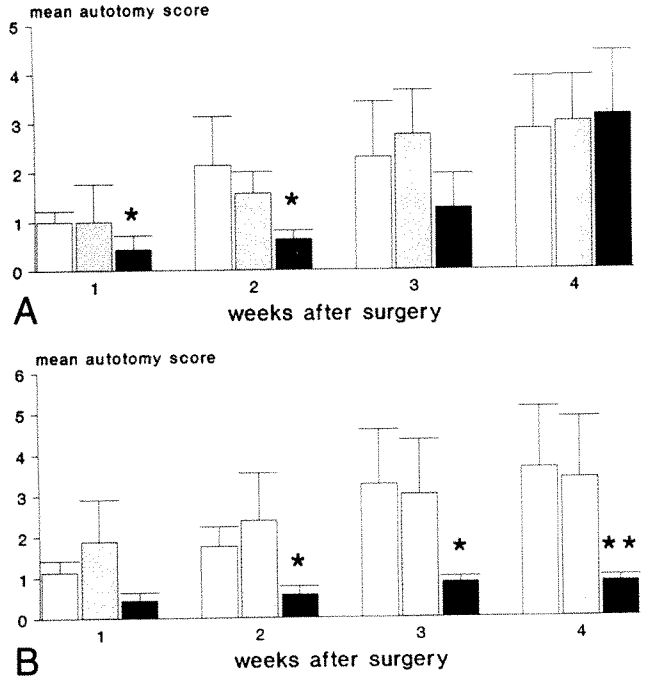


Figure 1. Postoperative course of autotomy after (**A**) sciatic section and (**B**) cervical dorsal rhizotomy. **Bars** indicate the mean value ± SEM. *$P < 0.05$; **$P < 0.01$; Mann-Whitney test versus control group. □, Saline; ▨, 5 mg·kg^{-1}·day^{-1} phenobarbital; ■, 10 mg·kg^{-1}·day^{-1} phenobarbital.

treated with phenobarbital, differences are statistically significant only between animals treated with phenobarbital (10 mg·kg^{-1}·day^{-1}) and control animals ($P < 0.05$; Mann-Whitney test). At the end of the observation period, almost all animals had begun autotomy of the denervated limb; the differences among groups were not significant. The average autotomy score increased smoothly in groups treated with saline solution and low doses of phenobarbital (Figure 1A). The differences between these two groups are not significant. However, animals treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital showed low autotomy scores during the first and second weeks, and there are statistically significant differences compared with control animals treated with saline solution ($P < 0.05$; Mann-Whitney test). In this group, autotomy increases within days after halting treatment with phenobarbital.

The day of onset of autotomy and the percentage of animals developing autotomy after dorsal rhizotomy are also shown in Table 1. Both groups treated with phenobarbital showed a delay in the average day of onset of autotomy compared with control animals, but only the difference between the control group and the group treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital is statistically significant ($P < 0.01$; Mann-Whitney test). As happens after sciatic section, at the end of the observation period almost all animals had begun autotomy of the denervated limb, and the differences among the groups were not significant. However, in the animals treated with larger doses of phenobarbital, there were no animals with severe autotomy (autotomy ≥5 points). The average autotomy score increased in the same way in groups treated with saline solution and low doses of phenobarbital (Figure 1B), and the differences between these two groups are not significant. However, animals treated with 10 mg·kg^{-1}·day^{-1} of phenobarbital displayed very low autotomy scores during the observation period. In this group, the mean autotomy score did not reach 1 point at any time. The differences between this group and the saline solution-treated group are statistically significant from the second week onward.

Pain Threshold in the Tail-Flick Test

The aim of this test was to determine whether phenobarbital has an analgesic effect on acute pain. Results of the tail-flick test for each experimental group are shown in Table 2. There were no significant

Table 2. Tail-Flick Latency After Intraperitoneal and Intrathecal Phenobarbital Injection

Group	Preinjection	Latency after phenobarbital injection		
		10 Min	20 Min	30 Min
Intraperitoneal				
Saline solution (n = 6)	2.2 ± 0.2	2.0 ± 0.3	1.9 ± 0.2	2.1 ± 0.2
1 mg (n = 10)	2.1 ± 0.1	2.1 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
2 mg (n = 5)	2.0 ± 0.3	2.3 ± 0.3	1.9 ± 0.1	1.8 ± 0.1
4 mg (n = 5)	2.4 ± 0.4	2.7 ± 0.3	1.9 ± 0.2	2.0 ± 0.0
8 mg (n = 5)	2.2 ± 0.1	2.9 ± 0.4	2.3 ± 0.2	2.3 ± 0.3
16 mg (n = 6)	2.2 ± 0.2	2.2 ± 0.2	2.0 ± 0.1	1.7 ± 0.1
Intrathecal				
Saline (n = 6)	3.1 ± 0.2	3.1 ± 0.3	3.3 ± 0.3	3.0 ± 0.2
100 μg (n = 6)	2.8 ± 0.3	3.7 ± 0.5	3.3 ± 0.6	3.2 ± 0.4
200 μg (n = 5)	3.5 ± 0.3	5.0 ± 0.6	4.7 ± 0.7	4.1 ± 0.6
500 μg (n = 8)	3.4 ± 0.2	5.9 ± 0.5*	4.4 ± 0.4*	4.2 ± 0.4*

Results are expressed as means ± SEM.
*P < 0.05, Wilcoxon test versus preinjection value.

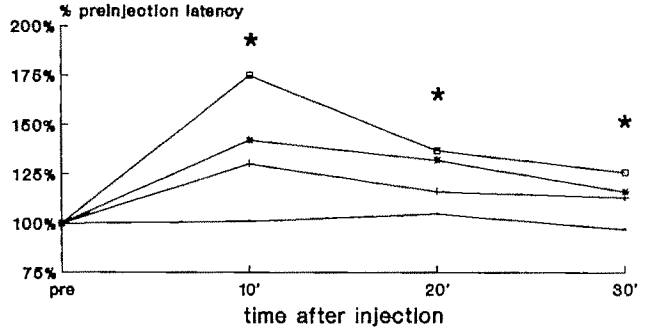


Figure 2. Latency in the tail-flick test after intrathecal administration of 100, 200, and 500 μg of phenobarbital. Latency is expressed as percentage change in relation to pretreatment values. There is a dose-related increase in the latency, with a significant difference after injection of 500 μg of phenobarbital. *P < 0.05; Wilcoxon test versus pretreatment values. —●—, saline; —+—, 100 μg phenobarbital; —*—, 200 μg phenobarbital; —□—, 500 μg phenobarbital.

changes in tail-flick latency after intraperitoneal administration of 1–16 mg of phenobarbital. The 16-mg dose produced somnolence a few minutes after the injection, but no other secondary effects were seen. Doses of 100 and 200 μg of intrathecal phenobarbital produced no significant changes in tail-flick latency, but after 500 μg, a significant increase was observed 10, 20, and 30 min after injection (P < 0.05, Wilcoxon test). Figure 2 shows the results of the tail-flick test after intrathecal administration of phenobarbital as a percentage of preinjection tests. There were no significant clinical findings after intrathecal injection. One rat developed a paresis of the lower limbs after an intrathecal injection of 100 μg of phenobarbital and was dropped from the study.

Pathological Findings

Specimens from all groups showed the same pathological changes in relation to the surgical procedures. There were no differences among neuromas or in the spinal cord at the level of the rhizotomy. Intrathecal catheters were surrounded by reactive tissue. No major lesions were observed in roots or spinal cord as a result of catheter placement.

Discussion

An understanding of the pathophysiology of deafferentation pain is an important objective if the successful treatment of this type of chronic pain is to be achieved clinically. Basic researchers have shown that deafferentation is followed by spontaneous firing in sensory pathway cells, namely, in dorsal root ganglion cells, dorsal horn, and nucleus cuneatus neurons, and also at the thalamic and cortical levels (4–7). The location of bursting neurons in the dorsal horn was anatomically placed by Albe-Fessard and Rampin (4) in layers IV and V; others found hyperactive cells in all of the layers of the dorsal horn (5). However, it is difficult to assign functional correlations, owing to the lack of peripheral receptive fields in deafferented animals. Clinical investigations (8–10) in patients with deafferentation pain showed similar hyperactivity in neurons in the dorsal horn of the spinal cord and in neurons in specific and intralaminar thalamic nuclei. These neurons show a spontaneous hyperactivity that resembles the electrical activity recorded in experimental alumina-induced epileptic foci (4,8,18). Moreover, the injection of alumina into the spinal cord subarachnoid space of the cat induces a painful dysesthesia with neuronal hyperactivity (18).

Anticonvulsant drugs have been used in the treatment of some types of pain, including trigeminal neuralgia and other types of neuralgic pain (19). Recently, some researchers pointed out that benzodiazepines, another type of drug with anticonvulsant activity, delivered by different routes, including intrathecal injection, have an analgesic effect on acute pain (16,20,21). Electrophysiologic studies suggest that benzodiazepines have a prevailing anticonvulsant activity that depresses the spontaneous hyperactivity of deafferented dorsal horn neurons, rather than a direct antinociceptive action that reduces or blocks C- or Aδ-evoked responses (22).

Given this background, it seems reasonable to attempt to prevent or reduce deafferentation pain by the use of anticonvulsant drugs. In our study we used long-term treatment with phenobarbital in an attempt to prevent autotomy behavior in the sciatic section and dorsal rhizotomy models of pain. The

pathophysiologic bases of these models are different. In the sciatic section model, at least two sources of nociceptive discharges have been implicated: spontaneous discharges from neuroma and dorsal root ganglia in the peripheral nervous system and hyperactive deafferented neurons in the sensory relays of the central nervous system (6,7). Dorsal cervical rhizotomy is followed by spontaneous hyperactivity in the central nervous system and has no peripheral component (4,5). Long-term phenobarbital treatment (10 $mg \cdot kg^{-1} \cdot day^{-1}$) reduces the autotomy score and also delays the day of onset of autotomy in both experimental models when compared with control groups. If autotomy is related to those proposed mechanisms, then the effect on autotomy behavior might be explained by the antiepileptic action of phenobarbital reducing the hyperexcitability of the cell membrane. Three mechanisms of action have been postulated for phenobarbital: at high concentrations, phenobarbital activates the γ-aminobutyric acid-related choride channels and reduces the sodium and calcium influx, but at therapeutic concentrations, phenobarbital enhances the postsynaptic response to γ-aminobutyric acid and blocks the excitatory response to glutamic acid (23,24). In our experience, changes in autotomous behavior are obtained with high doses of phenobarbital; however, reduction of autotomy could not be attributed to a sedative or hypnotic effect of phenobarbital. Treated rats were alert and showed a normal social behavior as did control rats receiving saline solution.

Results are better in deafferentation by dorsal root section than by sciatic section. The rhizotomy deafferentation syndrome should be more susceptible to phenobarbital, given the fact that it is entirely due to central hyperexcitability, whereas deafferentation after sciatic section adds peripheral mechanisms that are eventually less susceptible to the action of phenobarbital.

There have been few attempts to modify autotomy by means of an anticonvulsant drug. In 1977, Duckrow and Taub (25) demonstrated that intraperitoneal diphenylhydantoin reduced the incidence of self-mutilation when it was given at doses of >10 $mg \cdot kg^{-1} \cdot day^{-1}$. Albe-Fessard and Lombard (26) tested carbamazepine, clonazepam, and valproic acid in light doses, with inconclusive results. Our results also show a clear action of the long-term treatment with phenobarbital on autotomy. These findings suggest the possibility of reducing autotomy behavior in rats with the use of anticonvulsant drugs. However, when treatment is discontinued 10 days after sciatic section, autotomy increases, although there are no changes in animals that have had a rhizotomy.

Our results also indicate that the effect of phenobarbital on autotomy behavior is probably related more to its anticonvulsant properties than to any direct analgesic action of the drug. In our experience, only high doses of intrathecal phenobarbital increase the pain threshold in tests of acute pain. Anticonvulsant doses of phenobarbital are less than sedative or hypnotic doses, although the margin of safety is narrow (16,23). Potentially analgesic intraperitoneal doses were not reached in our short-term experiments, because 16 mg caused drowsiness and somnolence in the rat. However, 500 μg of intrathecal phenobarbital had a clear but weak analgesic action without secondary effects.

In conclusion, autotomous behavior after peripheral deafferentation in rats is delayed and reduced after long-term treatment with 10 $mg \cdot kg^{-1} \cdot day^{-1}$ of phenobarbital. From a clinical point of view, the administration of phenobarbital before deafferentation is only possible when this event is scheduled, such as amputations or ablative surgical procedures for the treatment of pain. The results of this study suggest that this analgesic action is related to the anticonvulsant activity of phenobarbital. Moreover, intrathecal phenobarbital has an analgesic action.

The authors thank the Department of Pharmacology of the Faculty of Medicine, University of Cádiz, for technical and scientific assistance. We are also grateful to Emilio de la Orden for his laboratory work.

References

1. Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb among American Veterans. Am J Phys Med 1983;62:227–38.
2. Sunderland S. Nerves and nerve injuries. 2nd ed. New York: Churchill Livingstone, 1978:421–58.
3. Melzack R. Phantom limb pain. Anesthesiology 1971;35:409–19.
4. Albe-Fessard D, Rampin O. Neurophysiological studies in rats deafferented by dorsal root sections. In: Nashold BS Jr, Ovelmen-Levitt J, eds. Deafferentation pain syndromes: pathophysiology and treatment. New York: Raven Ps, 1991:125–39.
5. Brinkhus HB, Zimmermann M. Characteristics of spinal dorsal horn neurons after partial chronic deafferentation by dorsal root transection. Pain 1983;15:221–36.
6. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal nerve and nerve injured rats. Pain 1983;17:321–39.
7. Wall PD, Gutnick M. Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. Exp Neurol 1974;43:580–93.
8. Loeser JD, Ward AA Jr, White JE. Chronic deafferentation of human spinal cord neurons. J Neurosurg 1968;29:48–50.
9. Hirayama T, Dostrovsky JO, Gorecki J. Recordings of abnormal activity in patients with deafferentation and central pain. Stereotact Funct Neurosurg 1989;52:120–6.
10. Rinaldi PC, Young RF, Albe-Fessard D, Chodakiewitz J. Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. J Neurosurg 1991;74:415–21.

11. Bach S, Noreng MF, Tjéllden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988; 33:297–301.
12. González-Darder JM, Barberá J, Abellán MJ. Effects of prior anaesthesia on autotomy following sciatic transection in rats. Pain 1986;24:87–91.
13. González-Darder JM, Barberá J, Abellán MJ, Mora A. Centro-central anastomosis in the prevention and treatment of painful terminal neuroma. An experimental study in the rat. J Neurosurg 1985;63:754–8.
14. Blumenkopf B, Lipman JJ. Studies in autotomy: its pathophysiology and usefulness as a model of chronic pain. Pain 1991; 45:203–10.
15. Coderre TJ, Grimes RW, Melzack R. Deafferentation and chronic pain in animals: an evaluation of evidence suggesting autotomy is related to pain. Pain 1986;26:61–84.
16. González-Darder JM, Gómez-Cárdenas E, Guerrero M, Segura-Pastor D, Gil-Salú JL. Intrathecal antiepileptic drugs in experimental epilepsy. Stereotact Funct Neurosurg 1991;57: 147–55.
17. González-Darder JM, Gómez-Cárdenas E, Segura-Pastor D, Carrasco MS. Acción analgésica y anticonvulsivante en la rata del midazolam administrado por via intratecal. Rev Esp Anestesiol Reanim 1990;37:261–4.
18. Loeser JD, Peirce KR. Intraspinal alumina injection: the relationship between epileptiform focus, root scarring and chronic pain. Pain 1978;5:245–52.
19. Swerdlow M. Anticonvulsant drugs and chronic pain. Clin Neuropharmacol 1984;7:51–82.
20. Niv D, Davidovich S, Geller E, Urca G. Analgesic and hyperalgesic effects of midazolam: dependence on route of administration. Anesth Analg 1988;67:1169–73.
21. Rattan AK, McDonald JS, Tejwani GA. Differential effects of intrathecal midazolam on morphine-induced antinociception in the rat: role of spinal opioid receptors. Anesth Analg 1991;73:124–31.
22. Clavier N, Lombard MC, Besson JM. Benzodiazepines and nociceptive dorsal horn neuronal activity in the rat spinal cord: antinociceptive or anticonvulsant effects? Pain 1990;5(Suppl): S224.
23. Kutt H. Mechanisms of action of antiepileptic drugs. In: Magnus O, Lorentz de Haas AM, eds. The epilepsies. Amsterdam: North Holland, 1974:621–63.
24. Bruni J, Albright PS. The clinical pharmacology of antiepileptic drugs. Clin Neuropharmacol 1984;7:1–34.
25. Duckrow RB, Taub A. The effect of diphenylhydantoin on self-mutilation in rats produced by unilateral multiple dorsal rhizotomy. Exp Neurol 1977;54:33–41.
26. Albe-Fessard D, Lombard MC. Animal models for pain due to central deafferentation. Methods of protection against this syndrome. Pain 1981;1(Suppl):S80.

Effects of Flumazenil on Intravenous Lidocaine-Induced Convulsions and Anticonvulsant Property of Diazepam in Rats

Masataka Yokoyama, MD, Kirk T. Benson, MD, Kasumi Arakawa, PhD, MD, and Hiroshi Goto, MD

Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, Kansas

We investigated the effect of flumazenil on intravenous (IV) lidocaine-induced convulsions with and without diazepam pretreatment in rats. Wistar rats (200–250 g) were divided into four groups of seven each and were pretreated with IV diazepam or normal saline solution at 6 min and flumazenil or normal saline solution at 3 min before lidocaine infusion. The control group received normal saline solution; the diazepam group received 0.2 mg/kg of diazepam and normal saline solution; the diazepam + flumazenil group received 0.2 mg/kg of diazepam and 0.1 mg/kg of flumazenil; and the flumazenil group received normal saline solution and 0.1 mg/kg of flumazenil. After surgical preparation and recovery from anesthesia, all groups received a continuous IV infusion of lidocaine (15 mg/mL) at a rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ until tonic/clonic convulsions occurred. The values of pH and blood gases were maintained within physiologic ranges. Heart rate was significantly decreased after 5 min of lidocaine infusion, but arterial blood pressure did not change until convulsions occurred in all groups. Pretreatment with diazepam alone increased both cumulative convulsant doses and plasma concentrations of lidocaine at the onset of convulsions. Flumazenil reversed these effects of diazepam. Pretreatment with flumazenil alone changed neither cumulative convulsant doses nor plasma concentrations of lidocaine at the onset of convulsions. Our data show that IV flumazenil reverses the anticonvulsant property of IV diazepam against lidocaine-induced convulsions and that flumazenil itself has no effect on lidocaine-induced convulsions in rats.

(Anesth Analg 1992;75:87–90)

Benzodiazepines are used widely as sedatives for premedication and for the induction and maintenance of anesthesia; however, sedative-hypnotic effects of benzodiazepines frequently persist postoperatively. Flumazenil, the first specific benzodiazepine receptor antagonist, is marketed in some countries and has received clinical attention as an effective antagonist of benzodiazepine-induced sedation (1,2). The different pharmacologic effects of benzodiazepines are reversed by different doses of flumazenil (3). It is unclear whether flumazenil antagonizes the anticonvulsant property of benzodiazepines. Furthermore, the effect of flumazenil on lidocaine-induced convulsions has not been reported. We used an awake-rat model of lidocaine-induced convulsions to determine whether flumazenil antagonizes the anticonvulsant effect of diazepam and whether flumazenil itself affects lidocaine-induced convulsions.

Methods

This study was approved by the institutional animal care committee. Animals fasted overnight (water was supplied ad libitum), and the experiments were performed between 1 and 5 PM.

Twenty-eight male Wistar rats weighing 200–250 g were anesthetized with halothane in oxygen during surgical preparation. One of the femoral arteries was cannulated with a polyethylene catheter for monitoring arterial blood pressure and heart rate and for blood sampling, and the femoral vein was also cannulated for infusion of drugs. The proximal ends of these catheters were tunneled subcutaneously to the posterior cervical region so the animals could move freely. Before emergence from anesthesia, the ani-

This work was presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1991.

Accepted for publication March 24, 1992.

Address correspondence to Dr. Yokoyama, Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, KS 66160-7415.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Hemodynamic Changes in the Four Study Groups

	Study group ($n = 7$)	Time				
		−1 Min	0 Min	1 Min	5 Min	IBC
HR (beats/min)	C	426 ± 10	419 ± 11	400 ± 18	343 ± 12[a–c]	344 ± 11[a–c]
	D	419 ± 6	429 ± 4	412 ± 8	366 ± 9[a–c]	340 ± 5[a–d]
	D + F	419 ± 5	426 ± 7	413 ± 9	351 ± 12[a–c]	331 ± 6[a–c]
	F	412 ± 14	414 ± 14	406 ± 15	346 ± 9[a–c]	326 ± 9[a–c]
MAP (mm Hg)	C	102 ± 1	103 ± 2	101 ± 2	100 ± 2	101 ± 3
	D	107 ± 2	107 ± 2	105 ± 4	105 ± 4	107 ± 3
	D + F	107 ± 3	103 ± 2	102 ± 2	102 ± 2	102 ± 2
	F	102 ± 2	100 ± 2	99 ± 1	97 ± 1	101 ± 2

HR, heart rate; MAP, mean arterial blood pressure; IBC, immediately before convulsions; C, control; D, diazepam; D + F, diazepam + flumazenil; F, flumazenil.
[a] $P < 0.01$ vs control.
[b] $P < 0.01$ vs 0 min.
[c] $P < 0.01$ vs 1 min.
[d] $P < 0.01$ vs 5 min.
Results are mean values ± SEM.

mals were placed in a plastic container to recover for 2 h before the experiment.

The animals were divided into four groups of seven each to receive either pretreatment with intravenous (IV) diazepam or normal saline solution at 6 min and IV flumazenil or normal saline solution at 3 min before lidocaine infusion. The control group (group C) received normal saline solution (1 mL/kg); the diazepam group (group D) received 0.2 mg/kg of diazepam in normal saline solution (1 mL/kg) and normal saline solution; the diazepam + flumazenil group (group D + F) received 0.2 mg/kg of diazepam in normal saline solution (1 mL/kg) and 0.1 mg/kg of flumazenil in normal saline solution (1 mL/kg); and the flumazenil group (group F) received normal saline solution and 0.1 mg/kg of flumazenil in normal saline solution (1 mL/kg). After pretreatment, all groups received a continuous IV infusion of lidocaine (15 mg/kg) at a rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ (0.053–0.067 mL/min) by infusion pump until tonic/clonic convulsions occurred. Total lidocaine doses from the beginning of infusion to the onset of convulsions were calculated for each animal as Infusion rate × Infusion time.

During lidocaine infusion, arterial blood pressure and heart rate were continuously monitored and recorded, and the animals were continuously observed for tonic/clonic convulsions.

Arterial blood, 0.2 mL, was withdrawn just before beginning the lidocaine infusion and 1.0 mL at the onset of convulsions to determine blood gas tensions, pH, and plasma concentrations of lidocaine. For determination of plasma concentrations of lidocaine, blood samples were centrifuged and the plasma frozen at −80°C until analyzed. Lidocaine concentrations were determined UV spectrophotometrically by high-performance liquid chromatography (HPLC); LC-6A (Shimadzu, Kyoto, Japan) and SPD-6A (Shimadzu) were used as pump and detector, respectively, in the HPLC system. We used the method of analysis introduced previously by Satoh (4). The analytic conditions were as follows: the column—Shim-Pack (ODS) 4.6 × 250 mm (Shimadzu); the mobile phase—0.05 M KH_2PO_4, 0.05 M K_2HPO_4/acetonitrile pH 4.0 (88:12 vol/vol).

Diazepam was diluted from the trade solution (Valium, Roche Laboratories, Nutley, N.J.) in normal saline solution to a concentration of 0.2 mg/mL. Flumazenil (Ro 15-1788, Roche Laboratories) was dissolved in normal saline solution with 1 drop of Tween 80 to a concentration of 0.1 mg/mL, according to the method of Le Gal La Salle and Feldblum (5).

Data obtained were expressed as mean values ± SEM. Statistically significant differences were determined by analysis of variance, followed by Duncan's method or Student's paired t-test; $P < 0.05$ was considered significant.

Results

Baseline heart rate and mean arterial blood pressure were similar in the four groups (Table 1). Heart rate was significantly decreased after 5 min of lidocaine infusion until the onset of convulsions in all groups. Mean blood pressure did not change until the onset of convulsions in all groups.

Baseline blood gas data (Table 2) in the four groups were similar. The blood gas values and pH in all groups were within physiologic ranges at the onset of convulsions.

Pretreatment with diazepam (group D) increased both the cumulative convulsant doses of lidocaine (54.9 ± 1.3 mg/kg, $P < 0.01$) and the plasma concentrations of lidocaine at the onset of convulsions

Table 2. Analysis of Arterial Blood Gases in the Four Study Groups

	Study group (n = 7)	Baseline	Convulsions
pHa	C	7.409 ± 0.007	7.411 ± 0.012
	D	7.400 ± 0.004	7.400 ± 0.007
	D + F	7.414 ± 0.006	7.406 ± 0.008
	F	7.424 ± 0.008	7.421 ± 0.008
Pao_2 (mm Hg)	C	80.6 ± 1.6	86.7 ± 3.4
	D	75.8 ± 1.1	79.7 ± 2.3
	D + F	78.0 ± 2.2	83.7 ± 3.1
	F	80.6 ± 1.9	90.3 ± 2.6[a]
$Paco_2$ (mm Hg)	C	34.9 ± 1.0	38.6 ± 0.9
	D	38.3 ± 1.2	39.0 ± 2.0
	D + F	35.7 ± 1.9	38.5 ± 1.9
	F	35.8 ± 1.0	37.6 ± 1.6
HCO_3 (mEq/L)	C	22.8 ± 0.8	24.1 ± 0.4
	D	23.6 ± 0.6	24.1 ± 1.3
	D + F	23.0 ± 1.2	24.1 ± 1.2
	F	23.4 ± 0.9	24.3 ± 1.2

C, control; D, diazepam; D + F, diazepam + flumazenil; F, flumazenil. Results are mean values ± SEM.
[a] $P < 0.01$ vs 0 min.

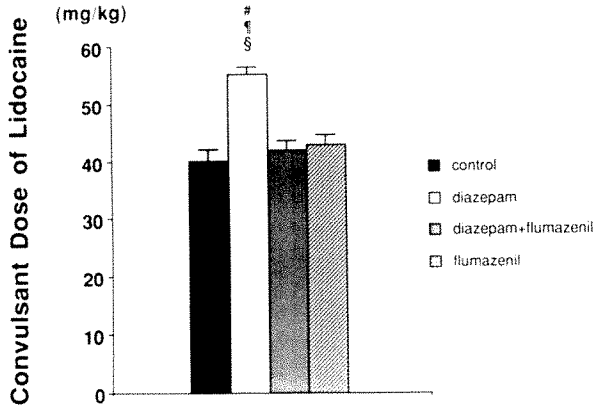


Figure 1. Convulsant dose of lidocaine in each group. Results are mean values ± SEM (n = 7). #$P < 0.01$ versus control; ¶$P < 0.01$ versus diazepam + flumazenil; §$P < 0.01$ versus flumazenil.

(15.3 ± 0.7 μg/mL, $P < 0.01$) compared with group C (40.0 ± 1.9 mg/kg and 10.8 ± 0.5 μg/mL, respectively) (Figures 1 and 2). The combination of diazepam and flumazenil (group D + F) and flumazenil alone (group F) affected neither cumulative convulsant doses of lidocaine (41.8 ± 1.6 and 42.8 ± 1.6 mg/kg, respectively) nor plasma concentrations of lidocaine at the onset of convulsions (11.5 ± 0.4 and 10.8 ± 0.4 μg/mL, respectively) compared with group C (Figures 1 and 2).

Discussion

Specific binding of ^{3}H-diazepam to crude synaptosomal fractions of rat cerebral cortex was inhibited

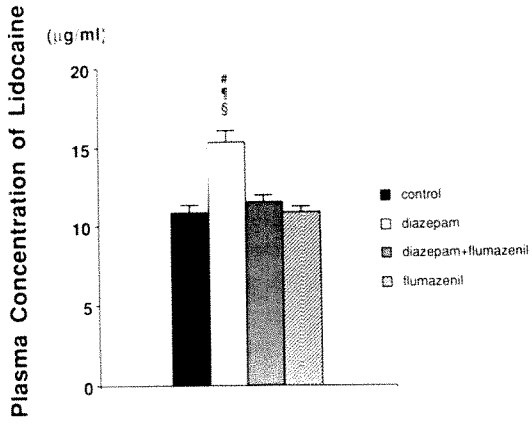


Figure 2. Plasma concentration of lidocaine at onset of convulsions in each group. Results are mean values ± SEM (n = 7). #$P < 0.01$ versus control; ¶$P < 0.01$ versus diazepam + flumazenil; §$P < 0.01$ versus flumazenil.

competitively by flumazenil at one-fourth the milligram dosage of ^{3}H-diazepam (6); however, a wide dose range of flumazenil has been used to successfully antagonize diazepam-induced sedation in vivo (2,3). Dodgson et al. (3) also reported that the dose of flumazenil required to antagonize diazepam-induced sedation might be different from that required to antagonize diazepam-induced amnesia. They speculated that there are several types of benzodiazepine receptors and that flumazenil has a greater affinity for the receptors that regulate psychomotor performance. Therefore, the dose of flumazenil antagonizing the anticonvulsant effect of diazepam might differ from that antagonizing the sedative or amnestic effect. Moreau et al. (7) reported that 10 mg/kg of intraperitoneal flumazenil reversed the anticonvulsant action of 3 mg/kg of intraperitoneal diazepam against convulsions induced by intracerebroventricular injection of *N*-methyl-D-aspartic acid in mice. Le Gal La Salle and Feldblum (5) reported that in rats fully kindled from repeated electrical amygdaloid stimulation, flumazenil (0.4–0.5 mg/kg) reversed the anticonvulsant effects of subcutaneous doses of 2 mg/kg of diazepam and that the anticonvulsant reversal effect remained the same with flumazenil doses up to 20 mg/kg. Thus, the anticonvulsant effect of diazepam was antagonized to the same extent by flumazenil from one-fourth to 10 times the diazepam dose. Although the methods in the studies cited differed, we selected 0.1 mg/kg of IV flumazenil for 0.2 mg/kg of IV diazepam.

In the initial trials, flumazenil was not considered to have its own pharmacologic effects (8); however, there are several recent reports that flumazenil has intrinsic actions. Bansky et al. (9) reported that IV flumazenil reversed hepatic coma in humans. Schöpf et al. (10) reported that 5 mg of IV flumazenil in-

creased the degree of anxiety. On the other hand, Scollo-Lavizzari (11) reported that 2.5 mg of IV flumazenil caused a marked reduction of epileptic potentials. Our study showed that 0.1 mg/kg of IV flumazenil had no effect on lidocaine-induced convulsions. Klotz and Kanto (8) reported that flumazenil had both weak and inverse agonist-like properties, depending on the basal conditions.

In clinical application, flumazenil is useful as an antagonist of excessive postoperative sedation caused by benzodiazepines and as an antidote to benzodiazepine intoxication. Nakazawa et al. (12) reported that flumazenil reverses lorazepam-induced cardiovascular depression; however, flumazenil can cause an unfavorable outcome when the effects of benzodiazepines are unnecessarily antagonized. Marchant et al. (13) reported a case of flumazenil-induced convulsions and ventricular tachycardia in a patient who had taken an overdose of both a tricyclic antidepressant and a benzodiazepine, and Scollo-Lavizzari (14) reported that convulsions were induced in an epileptic patient when IV flumazenil was administered to counteract the treatment of status epilepticus with diazepam, phenytoin, and phenobarbital. In our model, pretreatment with diazepam increased both the cumulative convulsant doses of lidocaine and the plasma concentrations of lidocaine approximately 40%. Flumazenil reversed the anticonvulsant effect of diazepam during lidocaine infusion. Our data suggest that flumazenil should be used with great care in patients who have received benzodiazepines to raise the threshold of local anesthetic toxicities during anesthesia and surgery and in patients who are receiving benzodiazepines for anticonvulsant therapy.

In conclusion, IV flumazenil reversed the anticonvulsant property of IV diazepam against lidocaine-induced convulsions, and flumazenil itself had no effect on lidocaine-induced convulsions in rats.

References

1. Skielboe M, Andersen P, Weber M, Jarnvig I-L, Jorgensen B, Christiansen C. Antagonism of diazepam sedation by flumazenil. Br J Anaesth 1989;63:554–7.
2. Ghoneim MM, Dembo JB, Block RI. Time course of antagonism of sedative and amnesic effects of diazepam by flumazenil. Anesthesiology 1989;70:899–904.
3. Dodgson MS, Skeie B, Emhjellen S, Wickstrom E, Steen PA. Antagonism of diazepam-induced sedative effects by Ro 15-1788 in patients after surgery under lumbar epidural block. Acta Anaesthesiol Scand 1987;31:629–33.
4. Satoh Y. Pharmacokinetics of lidocaine and monoethylglycinexylidide after the intratracheal administration of lidocaine. Masui 1988;37:1192–8.
5. Le Gal La Salle G, Feldblum S. Reversal of the anticonvulsant effects of diazepam on amygdaloid-kindled seizures by a specific benzodiazepine antagonist: Ro 15-1788. Eur J Pharmacol 1983;86:91–3.
6. Hunkeler W, Möhler H, Pieri L, et al. Selective antagonists of benzodiazepines. Nature 1981;290:514–6.
7. Moreau J-L, Pieri L, Prud'hon B. Convulsions induced by centrally administered NMDA in mice: effects of NMDA antagonists, benzodiazepines, minor tranquilizers and anticonvulsants. Br J Pharmacol 1989;98:1050–4.
8. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). Clin Pharmacokinet 1988;14:1–12.
9. Bansky G, Meier PJ, Ziegler WH, Walser H, Schmid M, Huber M. Reversal of hepatic coma by benzodiazepine antagonist (Ro 15-1788). Lancet 1985;1:1324–5.
10. Schöpf J, Laurian S, Le PK, Gaillard J-M. Intrinsic activity of the benzodiazepine antagonist Ro 15-1788 in man: an electrophysiological investigation. Pharmacopsychiatry 1984;17:79–83.
11. Scollo-Lavizzari G. The anticonvulsant effect of the benzodiazepine antagonist Ro 15-1788: an EEG study in 4 cases. Eur Neurol 1983;23:1–6.
12. Nakazawa K, Ohara S, Taneyama C, Unruh GK, Arakawa K. Benzodiazepine antagonist, Ro-15-1788, antagonizes cardiovascular depressant effect of lorazepam (abstract). Anesthesiology 1990;73:A619.
13. Marchant B, Wray R, Leach A, Nama M. Flumazenil causing convulsions and ventricular tachycardia. Br Med J (Clin Res) 1989;299:860.
14. Scollo-Lavizzari G. First clinical investigation of the benzodiazepine antagonist Ro 15-1788 in comatose patient. Eur Neurol 1983;22:7–11.

Does Preoperative Anxiety Influence Gastric Fluid Volume and Acidity?

Per E. Haavik, MD, Eldar Søreide, MD, Bjørn Hofstad, MD, and Petter A. Steen, MD, PhD

Departments of Anesthesiology, Ullevål Hospital and Rogaland Central Hospital, Stavanger, Norway

Preoperative anxiety may increase gastric fluid acidity and volume. To pursue this possibility we evaluated the relationship between peroral premedication, preoperative anxiety, and gastric content in 246 consecutive patients presenting for elective gynecologic surgery. All patients fasted overnight and received either flunitrazepam 1 mg, oxazepam 25 mg, or placebo with 20 mL of water on the morning of surgery in a randomized, double-blind fashion. The patients assessed relief of anxiety using a four-graded scale (excellent, good, fair, poor). Both flunitrazepam and oxazepam decreased anxiety ($P < 0.01$) compared with placebo. However, no correlations between type of premedication or level of anxiety and gastric contents were found. The proportion of patients with gastric fluid volume > 25 mL and pH < 2.5 was not significantly different in any of the groups studied. These results suggest that neither peroral benzodiazepine premedication nor preoperative anxiety have a clinically important impact on gastric content in patients presenting for elective gynecologic surgery.

(Anesth Analg 1992;75:91–4)

The main goal of premedication is to relieve anxiety (1). A variety of benzodiazepines, including diazepam, oxazepam, and flunitrazepam, reduce anxiety preoperatively (1–4). Ideally, premedication should also minimize the risk of aspiration pneumonitis. Gastric fluid volumes > 25 mL with a pH < 2.5 have been widely used as critical indicators for the development of aspiration pneumonitis and thus should be avoided (5–8).

Preoperative anxiety has been thought to delay gastric emptying and increase gastric acidity and is therefore considered a risk factor in connection with aspiration pneumonitis (9–11). If preoperative anxiety does have a negative impact on gastric fluid volume and pH, we hypothesized that the anxiolytic effects seen with various benzodiazepines would counteract this negative influence.

The purpose of this placebo-controlled study was to evaluate the relationship between peroral benzodiazepine premedication with flunitrazepam and oxazepam, preoperative anxiety, and gastric content in patients scheduled for elective gynecologic surgery.

This study was supported by a grant from Kabi Pharmacia, Norway.

Accepted for publication February 20, 1992.

Address correspondence to Dr. Søreide, Department of Anesthesiology, Rogaland Central Hospital, Armauer Hansensvei 20, 4011 Stavanger, Norway.

Methods

The study protocol was approved by the hospital ethical committee and performed in accordance with the latest edition of the Declaration of Helsinki. Only patients scheduled for surgery in general anesthesia with endotracheal intubation were selected. During a 6-mo period, written informed consent was obtained from 246 consecutive patients, aged 18–70 yr, ASA physical status I and II, all scheduled for gynecologic surgery. Patients with conditions known to affect gastric secretion and emptying, such as pain, second- or third-trimester pregnancy, a history of serious gastrointestinal disease, or obesity (defined as a body weight exceeding 120% of ideal body weight [IBW in kg = Height in cm − 100]) were excluded. Patients who had used psychotropic drugs during the last 10 days or suffered from alcohol or drug addiction were excluded as well.

Patients were randomized to receive either oxazepam 25 mg, flunitrazepam 1 mg, or placebo in a double-blind fashion. As no exact data were available to secure equipotent anxiolytic doses, the dosages recommended by the manufactures (oxazepam, Kabi Vitrum; flunitrazepam, Roche) were used. The study medications were placed in identical-looking soft gelatine capsules (capsugel). All patients fasted after midnight.

Inpatients were hospitalized the day before surgery and received a single dose of the study drug

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

between 9 and 11 PM the evening before surgery and the same compound the following morning at 7 AM. Outpatients received only the morning dose of the study drug. The premedication drugs were given with 20 mL of water at 7 AM. A minimum time lapse of 45 min from premedication to induction of anesthesia was required; no maximum length was set.

On arrival in the operating room, the patients gave a subjective assessment of the anxiolytic effect by answering the following question: "How do you evaluate the effect of the tablet on your anxiety now just before the operation; excellent, good, fair, or poor relief of anxiety?" Immediately after induction of anesthesia and orotracheal intubation, a multiorificed polyvinyl orogastric tube size 22F was inserted to 60 cm from the incisors, and correct position was verified by air insufflation and auscultation. The tube was withdrawn under intermittent suction, and all aspirated fluid was collected in a mucus trap polyvinyl bottle, which collapsed at negative pressures exceeding −60 mm Hg. The procedure was repeated once, and total volume, pH, and color of aspirate were recorded. Gastric pH was measured using Merck pH paper (12). The pH of the first 50 samples were double-checked with a calibrated Radiometer pH meter 28 to ensure that no systematic error was added to the study during the measurement of pH.

Results are given as means with standard deviation (SD), and range where appropriate. Statistical analysis was performed using one-way analysis of variance for parametric values and the χ^2-analysis to compare proportions of patients in the different groups. Differences were considered statistically significant when $P < 0.05$.

Results

Of the 246 patients studied, 152 were hospitalized for laparotomy (inpatients) and 94 patients were scheduled for ambulatory laparoscopy (outpatients). No differences in age distribution were noted in the three groups studied, with mean ages of 41 ± 14, 40 ± 14, and 41 ± 13 yr, respectively. The mean time from premedication to induction of anesthesia was 172 ± 101 (range 45–380 min) for flunitrazepam, 140 ± 88 (range 45–392 min) for oxazepam, and 171 ± 102 (range 45–380 min) for placebo ($P > 0.05$).

In Table 1 the patients' own ratings of anxiolytic effects are presented. Both flunitrazepam and oxazepam had a significantly better anxiolytic effect than placebo ($P < 0.01$). However, this difference in anxiolytic effect was not associated with any differences in gastric fluid volume and pH (Table 2).

The gastric fluid volumes and pH found in inpatients did not significantly differ from those found in outpatients (Table 2). Furthermore, no significant difference was found in pH between bile-stained, green aspirate and aspirate described as clear, bright yellow.

Table 1. Patients' Assessment of Anxiolytic Effect

Effect	Flunitrazepam	Oxazepam	Placebo	Sum
Excellent	15	16	6	37
Good	41	33	25	99
Fair	19	26	29	74
Poor	7	6	17	30
Sum	82	81	77	240

Flunitrazepam = oxazepam > placebo ($P < 0.01$).
Data lacking in six patients.

The proportion of patients with gastric fluid volumes > 25 mL and pH < 2.5 were not different for flunitrazepam, oxazepam, or placebo, whether the whole group was studied or inpatients or outpatients were studied separately (Table 3). To look at the effect of anxiety, independently of the drug given, the proportion of patients with gastric fluid volume > 25 mL and pH < 2.5 was compared between patients reporting poor or fair relief of anxiety and those reporting excellent or good relief (Table 3). No significant difference could be detected using these criteria either.

Discussion

This is the first placebo-controlled study of the relationship between premedication with peroral benzodiazepines, preoperative anxiety, and gastric content. Peroral premedication with benzodiazepines may influence gastric content in different ways. Some studies have shown an increase in gastric emptying and pH after intake of diazepam (13–16). These changes are probably due to effects on regulatory functions in the central nervous system (15) and could be present with other benzodiazepines as well. Further, the volume of fluid ingested with the premedication seems to play a role in determining the total gastric volume (5–8). In previous studies, 50–150 mL of water has been ingested. We allowed only 20 mL of water ("a sip of water") to be taken, thereby minimizing, if not eliminating, the effect of any water intake on the results.

When studying anxiolytic effects of drugs given preoperatively, the placebo effect should be separated from the pharmacologic effect (1). Madej and Paasku (1) believe the most reliable way to test for anxiolytic effects is to let the patient in some form assess the level of anxiety, as we did in the present study.

Preoperative anxiety has been asserted as a risk

Table 2. Volume and pH of Aspirated Liquids

	Flunitrazepam	Oxazepam	Placebo	All
All patients (n = 246)				
pH	2.0 ± 1.1	2.2 ± 1.1	2.4 ± 1.3	2.2 ± 1.2
Vol (mL)	23 ± 21	18 ± 18	18 ± 18	20 ± 18
Inpatients (n = 152)				
pH	2.1 ± 1.1	2.1 ± 1.2	2.3 ± 1.3	2.2 ± 1.2
Vol (mL)	22 ± 19	19 ± 17	23 ± 13	19 ± 16
Outpatients (n = 94)				
pH	2.0 ± 0.9	2.1 ± 1.1	2.4 ± 1.4	2.2 ± 1.2
Vol (mL)	25 ± 24	15 ± 13	22 ± 23	21 ± 20

Vol, volume.
There were no statistically significant differences between any of the listed groups ($P > 0.1$).

Table 3. Proportion of Patients With Gastric Volume > 25 mL and pH < 2.5

	Premedication				Relief of anxiety	
	Flu (n = 85)	Oxa (n = 88)	Pla (n = 73)	All (n = 246)	Excellent–good	Fair–poor
All patients (n = 246)	26/85 (31%)	21/88 (24%)	18/73 (25%)	65/246 (26%)	40/141 (28%)	24/103 (23%)
Inpatients (n = 152)	16/52 (31%)	13/55 (24%)	9/45 (20%)	38/152 (25%)	22/92 (24%)	15/59 (25%)
Outpatients (n = 94)	10/33 (30%)	8/33 (24%)	9/28 (32%)	27/94 (29%)	18/49 (37%)	9/44 (21%)

Flu, flunitrazepam; Oxa, oxazepam; Pla, placebo.
There were no statistically significant differences ($P > 0.1$) between any of the listed groups.

factor in connection with gastric content and aspiration pneumonitis (9,17). As previously reported (4), we found that flunitrazepam had a better overall anxiolytic effect than oxazepam and placebo. However, with the dosages used we could not detect any differences in gastric fluid volume and acidity between patients receiving flunitrazepam, oxazepam, or placebo. Neither could we find any differences in gastric contents between patients reporting good versus those reporting poor relief of anxiety, irrespectively of which drug they had received. Hence, our results do not support the existence of any association between the level of preoperative anxiety and gastric fluid volume and pH. One could speculate that the doses given where too small to achieve adequate anxiolysis and thereby significant effects on gastric fluid volume and pH. However, previous studies have not shown significant differences in anxiolytic effect between flunitrazepam 2 mg and 1 mg (3), or between flunitrazepam 1 mg and oxazepam 30 mg (2). Further, the values for gastric fluid volume and pH found with oxazepam 25 mg corresponded very well to the results in an earlier study where twice as much oxazepam (50 mg) was given (18).

Perhaps we need to better differentiate various types of anxiety in order to define patients in whom preoperative anxiety may influence gastric content. Simpson and Stakes (11) found that "gastric stasis occurred only in patients with a low predisposition to anxiety who became apprehensive whilst awaiting surgery." Our study did not make such distinctions possible. On the other hand, the rate of gastric emptying is just one of the many factors determining the volume of gastric fluid present at induction of anesthesia.

Interestingly, we did not observe any differences in gastric fluid volume and pH between inpatients, all scheduled for laparotomy, and outpatients, all scheduled for laparoscopy. Our findings contrast with the long-held assumption that outpatients as a group have increased gastric volumes (9,17). Similar to Brock-Utne et al. (19), we did not find bile-stained aspirate to be more alkaline than clear aspirate.

The accuracy of blind aspiration for studies of gastric content has been questioned by several authors (20,21) and has been a source of discussion in numerous studies (5–8,13). We used a larger multiorificed gastric tube (22F) than was used in many previous studies (5–8). Further, the suction system

was modified to prevent excessive negative pressure and sticking of the tube to the gastric wall. We believe these measures, together with the fact that one investigator performed the majority of aspirations, minimized the systemic error of blind aspiration in our study. We used Merck pH paper for the pH measurements, which has a high degree of accuracy compared with electronic pH meters (12,19), something that is in accordance with our own experience.

In summary, the results of this placebo-controlled study suggest that neither premedication with flunitrazepam and oxazepam in the present dosages nor the level of preoperative anxiety have any notable effects on gastric fluid volume and acidity. The mean gastric pH was <2.5 in all groups studied. Large proportions of patients in all groups had a combination of gastric fluid volume and acidity disposing for aspiration pneumonitis should regurgitation occur. Other measures than relieving preoperative anxiety must therefore be considered if the risk of aspiration pneumonitis is to be minimized.

References

1. Madej TM, Paasku RT. Anesthetic premedication: aims, assessment and methods. Can J Anaesth 1987;34:259–73.
2. Pakkanen A, Kangas L, Kanto J. A comparative study on the clinical effects of flunitrazepam and oxazepam as oral premedication. Int J Clin Pharmacol Ther Toxicol 1981;19:275–8.
3. Male CG, Lim YT, Male M, et al. A comparison of three benzodiazepines for oral premedication in minor gynaecological surgery. Br J Anaesth 1980;52:429–35.
4. Hofstad B, Haavik PE, Wickstrøm E, Steen PA. Benzodiazepines as oral premedication. A comparison between oxazepam, flunitrazepam and placebo. Acta Anesthesiol Scand 1987;31:295–9.
5. Maltby JR, Sutherland AD, Sale JP, et al. Preoperative oral fluids: is a five-hour fast justified prior to elective surgery? Anesth Analg 1986;65:1112–6.
6. Manchikanti L, Canella MC, Hohlbein L, et al. Assessment of effect of various modes of premedication on acid aspiration risk factors in outpatient surgery. Anesth Analg 1987;66:81–4.
7. Brocks K, Jensen S, Schmidt JF, et al. Gastric content and pH after oral premedication. Acta Anesthesiol Scand 1987;31: 448–9.
8. Hardy JF. Large volume gastro-esophagal reflux: a rationale for risk reduction in the preoperative period. Can J Anaesth 1988;35:162–73.
9. Lichtor JL. Psychological preparation and preoperative medication. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1990:913.
10. Guyton AC. Textbook of medical physiology. 7th ed. Philadelphia: Saunders, 1986:774–8.
11. Simpson KH, Stakes AF. Effect of anxiety on gastric emptying in preoperative patients. Br J Anaesth 1987;59:540–4.
12. Chaffe A. Which pH paper? Br J Anaesth 1987;59:1189–91.
13. Hjortsø E, Mondorf T. Does oral premedication increase the risk of gastric aspiration? Acta Anaesthesiol Scand 1982;26: 505–6.
14. Birnbaum D, Karmelli F, Tefera M. The effect of diazepam on human gastric secretion. Gut 1971;12:616–8.
15. Schurizek BA, Kraglund K, Andreasen, et al. Gastrointestinal motility and gastric pH and emptying following ingestion of diazepam. Br J Anaesth 1988;61:712–9.
16. Lehot JJ, Delat-Besson R, Bastien O, et al. Should we inhibit gastric acid secretion before cardiac surgery? Anesth Analg 1990;70:185–90.
17. Ong BY, Palahniuk RJ, Cumming M. Gastric volume and pH in out-patients. Can Anaesth Soc J 1978;25:36–9.
18. Søreide E, Reiestad F, Strømskag KE, et al. Oral oxazepam vs. intramuscular morphine-hyoscine for premedication: a study of gastric content using fibre-optic gastroscopy. Eur J Anaesthesiol 1990;7:375–80.
19. Brock-Utne JG, Rout C, Moofley J, et al. Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing caesarean section. Br J Anaesth 1989;62:397–401.
20. Adelhøj B, Petring OU, Hagelsten JO. Inaccuracy of peranesthetic gastric intubation for emptying liquid stomach contents. Acta Anaesthesiol Scand 1986;30:41–3.
21. Taylor WJ, Champion MC, Barry AW, et al. Measuring gastric contents during general anaesthesia: evaluation of gastric blind aspiration. Can J Anaesth 1989;36:51–4.

Effects of Single-Dose Intravenous Omeprazole and Ranitidine on Gastric pH During General Anesthesia

Peter G. Atanassoff, MD, Eli Alon, MD, and Thomas Pasch, MD

Department of Anesthesiology, University Hospital, Zurich, Switzerland

We conducted a comparative trial of the gastric proton pump inhibitor omeprazole and the H_2-receptor antagonist ranitidine on gastric pH in 50 adult patients scheduled for elective gynecologic surgery. The drugs were administered intravenously in random fashion after induction of general anesthesia and placement of a gastric electrode for continuous pH monitoring. The two drugs caused significant increases in gastric pH that did not differ significantly when compared with one another, yet there were significant differences from the control group, which did not receive either of the two drugs. A gastric pH of 2.5 was reached within median 34 and 26 min after administration of omeprazole (40 and 80 mg, respectively) and within median 32 and 26 min after administration of ranitidine (50 and 100 mg, respectively). After injection of omeprazole, a gastric pH of 3.5 was reached after median 41 and 34 min; injection of ranitidine (50 and 100 mg) produced a pH of 3.5 after median 43 and 48 min, respectively. We conclude that the intravenous administration of a single dose of omeprazole or ranitidine causes a similar increase, both in magnitude and time of onset, in gastric pH during general anesthesia.

(Anesth Analg 1992;75:95–8)

The aspiration of gastric contents during general anesthesia is still a major complication associated with a high morbidity and mortality. A gastric pH <2.5 and a volume of ≥25 mL are considered critical factors for the development of pulmonary damage in adults (1); low-volume pulmonary aspirates (0.3 mL/kg) with extremely low pH (1.0) resulted in a high mortality rate (90%) in rats (2). Subsequent investigations in animals have demonstrated that pH is more important than volume in determining lung injury and mortality (2,3). Among the various methods that have been investigated to reduce pulmonary injury after aspiration of gastric contents is the administration of drugs capable of increasing the pH or decreasing the volume of gastric juice, or both.

The goal of this investigation was to compare the increase of gastric pH under the influence of the well-established H_2-receptor antagonist ranitidine and omeprazole, a comparably new compound that has thus far proved highly effective in the treatment of postoperative bleeding from stress ulcers (4) and acid-related gastrointestinal diseases (5).

Methods

Fifty female patients (ASA physical status I and II) scheduled for elective gynecologic surgery were studied. Operations consisted of genital, lower abdominal, and breast surgery. No patient had a history of gastrointestinal disease or was taking drugs known to influence gastric acidity or volume. Obese patients were excluded from the study (body weight 20% above the ideal weight was defined as obesity). Informed consent was obtained in all cases. The study was approved by the Ethical Commitee of the University Hospital of Zurich.

All patients were hospitalized before the operation and had been fasting since midnight. Surgery was started early in the morning. The anesthetic technique was standardized. Premedication consisted of midazolam (5 mg IM) 45 min before anesthesia. Thiopental (4–6 mg/kg IV) was administered for induction of anesthesia and succinylcholine (1.5 mg/kg IV) to facilitate orotracheal intubation; enflurane and 70% nitrous oxide in oxygen as well as pancuronium for muscle relaxation were administered for maintenance of anesthesia. After intubation, a nasogastric tube was inserted into the stomach, and gastric contents were evacuated. Intragastric pH was mea-

This work was presented at the 66th Congress of the International Anesthesia Research Society Annual Meeting, San Francisco, California, March 13–18, 1992.

Accepted for publication March 16, 1992.

Address correspondence to Dr. Atanassoff, Department of Anesthesiology, University Hospital, Rämistrasse 100, 8091, Zurich, Switzerland.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Clinical Characteristics of the Five Study Groups

Study group	Age (yr)	Weight (kg)	Height (cm)
Omeprazole			
40 mg (n = 10)	51 ± 13 (31–64)	66 ± 10 (49–80)	164 ± 8 (155–180)
80 mg (n = 10)	45 ± 15 (23–63)	71 ± 13 (47–85)	168 ± 10 (154–184)
Ranitidine			
50 mg (n =10)	43 ± 13 (25–61)	60 ± 12 (51–82)	163 ± 11 (152–176)
100 mg (n = 10)	43 ± 14 (24–59)	62 ± 12 (50–78)	162 ± 8 (153–178)
Control (placebo) (n = 10)	46 ± 14 (28–65)	73 ± 10 (60–85)	171 ± 8 (162–180)

Data are presented as mean values ± SD; numbers in parentheses are ranges.

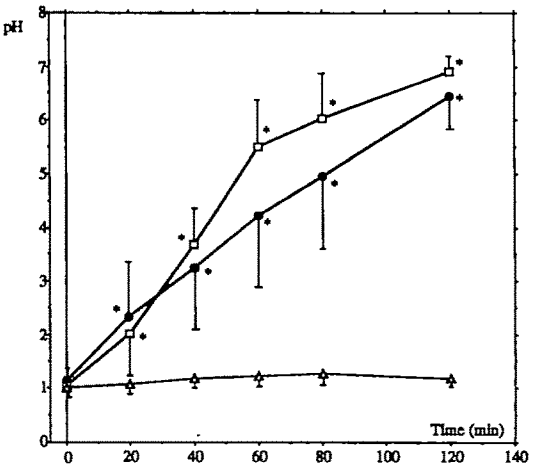


Figure 1. Development of gastric pH after injection of 40 and 80 mg of omeprazole. Data are presented as mean values ± SD. □, Omeprazole 80 mg; ●, omeprazole 40 mg; △, baseline. *P < 0.05 vs baseline.

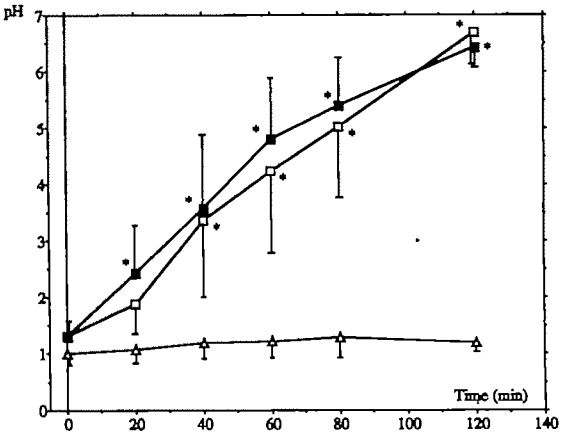


Figure 2. Increase in gastric pH after injection of 50 and 100 mg of ranitidine. Data are presented as mean values ± SD. ■, Ranitidine 100 mg; □, ranitidine, 50 mg; △, baseline. *P < 0.05 vs baseline.

sured with a miniaturized glass electrode connected to a solid-state recorder (Gastrograph Mark II, Medical Instruments Corporation, Switzerland) that printed data at 6-min intervals. Calibration was performed with buffer solutions of 7.00, 4.01, and 1.679 at room temperature. After each run, calibration was repeated for assessment of electrode accuracy and stability. An electrode drift of <0.1 pH units was considered acceptable. The electrode was advanced transnasally into the patient's stomach for continuous intragastric pH monitoring. Its proper position was verified by a sudden, sharp decrease in pH at the border of the esophagus and stomach; pH profiles were established for the duration of 2 h during general anesthesia.

The patients were randomly assigned to five groups of 10 patients each. Group A received omeprazole (40 mg), group B omeprazole (80 mg), group C ranitidine (50 mg), and group D ranitidine (100 mg). All anesthetics were administered intravenously immediately after placement of the gastric electrode. A control (placebo) group did not receive either of the two drugs.

For statistical comparison, the sum of individual measurements for all rating points was first calculated; this was followed by the multigroup Kruskal-Wallis test to examine differences between the groups. Pairwise comparisons among the treatment groups were made according to Nemenyi. Results were considered statistically significant if $P < 0.05$.

Results

Clinical characteristics of the patients with regard to age, weight, and height were comparable in the five groups (Table 1). Both doses of omeprazole (Figure 1) and ranitidine (Figure 2) increased gastric pH. After 40 min, three patients in group A, two in group B, three in group C, and three in group D failed to reach a gastric pH of 2.5. Complete failure occurred in only one patient in group C. Figure 3 shows median (range) pH 2.5 and 3.5 values versus time. With omeprazole 40 and 80 mg intravenously a gastric pH of 2.5 was reached after 34 min (range 8–60) and 26 min (range 10–57), respectively. Ranitidine 50 and 100 mg produced a gastric pH of 2.5 after 32 min (range 7–75) and 26 min (range 12–60), respectively. With omeprazole (40 and 80 mg IV), a pH of 3.5 was reached after 41 min (range 16–87) and 34 min (range 19–68), respectively. With ranitidine (50 and 100 mg IV), a pH of 3.5 was reached after 43 min (range 24–84) and 48 min (range 16–82), respectively.

There were no significant differences in the four

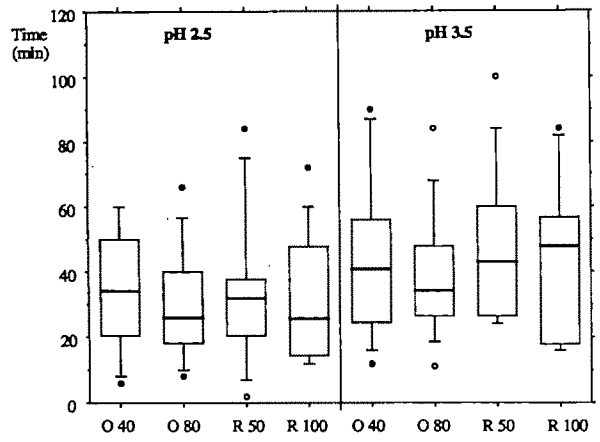


Figure 3. Gastric pH 2.5 and 3.5 plotted versus time. *Box:* Whisker plots present median values of the first time at which the patients in all treatment groups reached gastric pH of 2.5 and 3.5. The median is shown as a *solid horizontal line* surrounded by a *box* that represents the two quartiles (25th and 75th). *Whiskers* above and below the box indicate the furthest value within one interquartile distance from the quartile. Values outside this range are shown separately. O 40, omeprazole 40 mg; O 80, omeprazole 80 mg; R 50, ranitidine 50 mg; R 100, ranitidine 100 mg.

study groups when compared with one another, yet for most rating points, 80 mg omeprazole yielded the highest and 40 mg omeprazole the lowest mean pH values. The four treatment groups differed statistically significantly compared with the control group. Apart from baseline values, patients in groups A, B, and D showed a statistical difference from the placebo group at all times ($P < 0.05$); the same was true for ranitidine (50 mg) at 40, 60, 80, and 120 min ($P < 0.05$).

Discussion

Attempts to reduce intragastric acidity rely on various H_2-receptor antagonists or antacids. The literature describes a gastric pH of <2.5 and a volume that exceeds 0.4 mL/kg or 25 mL as critical factors for the development of pulmonary damage after aspiration in adults (1,6). Low-volume pulmonary aspirates (0.3 mL/kg) with extremely low pH (1.0) resulted in a high (90%) mortality rate in rats (2). Based on this definition, 17%–64% of patients who have been fasting are said to be at risk before elective surgery (7–9); an even higher percentage of patients are at potential risk if Crawford's (10) suggestion of a limit of 3.5 is accepted. Serious lung injury has been reported (11) in a patient who aspirated material with a pH of 3.5. Placement of an electrode into the stomach permits continuous monitoring of intragastric pH development under the influence of ranitidine and omeprazole. The reproducibility of this technique during standard time periods is excellent, and important changes of acidity are accurately detected (12). A drift of only 0.11 ± 0.01 pH units/24 h is described in the literature (13). Previous studies (14–16) had to exclude patients because gastric samples could not be obtained, mainly owing to inadequate gastric volume.

Ranitidine has been used successfully in reducing gastric pH and lung injury should aspiration occur. This drug is described as a more active H_2-receptor antagonist than its predecessor cimetidine (14). No side effects have been reported after single doses of ranitidine (14), which we observed in our study as well. The intravenous dose of 50 mg administered after induction of general anesthesia was just as effective as 100 mg in altering gastric pH to a final value of median 6.7 and 6.3, respectively, except that there was a slower increase for the 50-mg dose, with one patient failing completely. Median times of 32 and 26 min were necessary to increase the gastric pH to 2.5, the range believed to be associated with the risk of aspiration pneumonitis. This is in contrast to Durrant and Strunin (14), who mention a minimal effective time for H_2-receptor antagonists administered either orally or intravenously of 45 min. To meet Crawford's criterion of a pH of 3.5, 43 and 48 min were necessary.

Omeprazole is a comparably new compound that produces a more prolonged suppression of gastric acid secretion than H_2-receptor antagonists (16) because it remains in the gastric mucosa for 16–48 h (5). Like ranitidine it is effective in treating acid-related gastrointestinal diseases but with better results in less time (17–19). Large doses of ranitidine were unable to influence gastrointestinal bleeding, which could be stopped in most cases when treatment was switched to omeprazole (80 mg IV) (9). The drug can produce almost total inhibition of gastric acid secretion (20,21). Omeprazole is a substituted benzoimidazole and as such is a specific inhibitor of the proton pump H^+,K^+-ATPase. This enzyme acts at the final step in the acid-secreting pathway by exchanging luminal K^+ for cellular H^+ and is found only in the parietal cell. Omeprazole has no effect on other H^+-secreting cells in the body. Serious side effects have not been reported, possibly because its action is so selective (15). Likewise, we did not observe any side effects in our patients. The 40- and 80-mg dose, given intravenously after induction of general anesthesia, altered gastric pH significantly when compared with controls at all rating points recorded thereafter, but the two dosages did not differ significantly when compared with one another. At most rating points, however, 80 mg of omeprazole yielded the highest and 40 mg the lowest mean pH values, with ranitidine (50 and 100 mg) in between. After omeprazole (80 mg IV) and ranitidine (50 mg IV) administered as bolus and

continuous infusion to unanesthetized volunteers, the drugs were also well tolerated and showed a marked reduction in gastric acidity (22,23).

Many investigations have thus far centered on the oral administration of omeprazole: 80 mg the evening before surgery failed to increase gastric pH above 2.5 in 7 of 20 obstetric patients (24), whereas 40 mg the evening before and on the morning of cesarean section met this criterion (16). A pH of 2.5 was reached after 34 and 26 min with the 40- and 80-mg doses, respectively, in all of our patients, indicating that both doses are suitable for rapidly altering gastric pH. The maximal pH values reached were 6.5 and 6.9 after 2 h.

The data suggest that both ranitidine and omeprazole administered intravenously during general anesthesia cause a continuous increase in gastric pH. This increase did not differ significantly either between the two drugs or the different doses used in our investigation.

Both compounds are equally suitable for increasing gastric pH above the level believed to be associated with a potential risk for aspiration pneumonitis. Although the data were collected intraoperatively under the influence of a general anesthetic, it is highly probable that similar results would have been obtained were intravenous omeprazole and ranitidine administered preoperatively in unanesthetized patients.

References

1. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–68.
2. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration—effects of volume and pH in the rat. Anesth Analg 1984;63:665–8.
3. Kennedy TP, Johnson KJ, Kunkel RG, Ward PA, Knight PR, Finch JS. Acute aspiration lung injury in the rat: biphasic pathogenesis. Anesth Analg 1989;69:87–92.
4. Brunner G, Chang J. Intravenous therapy with high doses of ranitidine and omeprazole in critically ill patients with bleeding peptic ulcerations of the upper gastrointestinal tract: an open randomized controlled trial. Digestion 1990;45:217–25.
5. Anonymous. Omeprazole (editorial). Lancet 1987;2:1187–8.
6. Bannister WK, Sattilaro AJ. Vomiting and aspiration during anesthesia. Anesthesiology 1962;23:251–64.
7. Manchikanti L, Marrero TC, Roush JR. Preanesthetic cimetidine and metoclopramide for acid aspiration prophylaxis in elective surgery. Anesthesiology 1984;61:48–54.
8. Sutherland AD, Maltby JR, Sale JP, Reid CRG. The effect of preoperative oral fluid and ranitidine on gastric fluid volume and pH. Can J Anaesth 1987;34:117–21.
9. Stoelting RK. Gastric fluid pH in patients receiving cimetidine. Anesth Analg 1978;57:675–7.
10. Crawford S. Cimetidine in elective caesarean section. Anaesthesia 1981;36:641–2.
11. Taylor G. Acid pulmonary aspiration syndrome after antacids. A case report. Br J Anaesth 1975;47:615–7.
12. Merki HS, Witzel L, Walt RP, et al. Double blind comparison of the effects of cimetidine, ranitidine, famotidine, and placebo on intragastric acidity in 30 volunteers. Gut 1988;29:81–4.
13. Merki HS. Assessment of intragastric acidity in man: modern aspects and reproducibility of intragastric pH monitoring. In: Mignon M, Galpiche JP, eds. Control of acid secretion. Paris: John Libbey Eurotext, 1988:91–7.
14. Durrant JM, Strunin L. Comparative trial of the effect of ranitidine and cimetidine on gastric secretion in fasting patients at induction of anaesthesia. Can Anaesth Soc J 1982;29:446–51.
15. Ewart MC, Yau G, Gin T, Kotur CF, Oh TE. A comparison of the effects of omeprazole and ranitidine on gastric secretion in women undergoing elective caesarean section. Anaesthesia 1990;45:527–30.
16. Gin T, Ewart MC, Yau G, Oh TE. Effect of oral omeprazole on intragastric pH and volume in women undergoing elective caesarean section. Br J Anaesth 1990;65:616–9.
17. Lauritzen K, Rune SJ, Bytzer P. Effect of omeprazole and cimetidine on duodenal ulcer. N Engl J Med 1985;312:958–61.
18. Bardhan KD, Bianchi Porro G, Bose K. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. J Clin Gastroenterol 1986;8:408–13.
19. Walan A, Bader JP, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989;320:69–75.
20. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin acid secretion in man. Gut 1983;24:270–6.
21. Prichard PJ, Yeomans ND, Mithaly GW, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 1985;88:64–9.
22. Sackier JM, Halliday K, Sprott P, et al. The effects of intravenous omeprazole on 24 h gastric secretion in healthy subjects. Comparisons of continuous and intermittent infusions. A pilot study. Eur J Gastroenterol Hepatol 1991;3:679–84.
23. Merki HS, Hunt RH, Walt RP, et al. A new programmable infusion pump for individual control of intragastric pH: validation and effect of ranitidine. Eur J Gastroenterol Hepatol 1991;3:9–13.
24. Moore J, Flynn RJ, Sampaio M, Wilson CM, Gillon KRW. Effect of single dose omeprazole on intragastric acidity and volume during obstetric anaesthesia. Anaesthesia 1989;44:559–62.

Ketorolac Does Not Decrease the MAC of Halothane or Depress Ventilation in Rats

George F. Rich, MD, PhD, Richard Schacterle, MS, Jeffrey C. Moscicki, MS, Cosmo A. DiFazio, MD, PhD, and J. Milton Adams, PhD

Departments of Anesthesiology and Biomedical Engineering, University of Virginia Health Sciences Center, Charlottesville, Virginia

To determine the effects of intravenous (IV) ketorolac on anesthesia and the mechanisms involved, we evaluated its effects on minimum alveolar anesthetic concentration (MAC) and ventilation in halothane-anesthetized rats. Ketorolac in clinical (0.2 and 2 mg/kg) and large (20 and 40 mg/kg) IV doses did not affect the MAC of halothane (0.82% ± 0.02%). Resting end-tidal CO_2 tension (5.1% ± 0.1%) and the slope of the CO_2 response curves (70 ± 6 $mL \cdot min^{-1} \cdot \%^{-1}$) were also unaffected by IV ketorolac. The mean arterial blood pressure did not significantly change after ketorolac in doses of 0.2, 2, or 20 mg/kg but decreased significantly ($P < 0.05$) after 40 mg/kg (placebo 99 ± 8 mm Hg; ketorolac 87 ± 6 mm Hg). This study demonstrates that MAC, ventilation, and mean arterial blood pressure are unaffected by clinical doses of IV ketorolac. Furthermore, the lack of effect on MAC and ventilation from larger doses suggests that ketorolac does not have mechanisms of action in the central nervous system.

(Anesth Analg 1992;75:99–102)

Ketorolac, a nonsteroidal antiinflammatory drug, is useful as an analgesic during the perioperative period (1–4). Some nonsteroidal antiinflammatory drugs, including ketorolac, have central nervous system effects, including sleepiness (5–8); however, studies with oral doses of ketorolac in rodents suggest that ketorolac lacks central nervous system effects (9). It is not known whether intravenous (IV) ketorolac has significant central nervous system effects that could produce a decrease in anesthetic requirements. We hypothesized that if ketorolac works, in part, through central pathways, then a reduction in the minimum alveolar anesthetic concentration (MAC) of halothane should occur. We therefore evaluated the changes in the MAC of halothane in rats after clinical (0.2 and 2 mg/kg) and large (20 and 40 mg/kg) doses of IV ketorolac.

Small intramuscular doses of ketorolac do not cause respiratory depression in unanesthetized volunteers (10) or when combined with propofol anesthesia (11). It is not known whether IV ketorolac, particularly in large doses, has central nervous system analgesic effects that may be associated with respiratory depression. To determine the respiratory depressant effects of clinical and large doses of IV ketorolac, we measured the resting end-tidal CO_2 ($ETCO_2$) and CO_2 respiratory response curves in halothane-anesthetized rats.

Methods

Eighteen male Sprague-Dawley rats (290–340 g) were anesthetized with halothane and oxygen in a plastic chamber. A 14-g polyethylene endotracheal tube was inserted by means of a tracheostomy for airway control. The right femoral vein was cannulated for administration of IV ketorolac. The right femoral artery was cannulated for continuous mean arterial blood pressure (MAP) monitoring and arterial blood gas sampling. The rats were positioned supine on a warmer designed to maintain normothermia, as measured by rectal temperature.

The endotracheal tube was attached to a small Mapleson D circuit, and 12 rats were allowed to ventilate spontaneously. Anesthesia was maintained with 1% halothane and O_2. A pneumotachometer (Silverman screen), attached to the endotracheal tube, was used to measure respiratory frequency (f) and tidal volume (V_T). Minute ventilation (V_E) was calculated by $f \times V_T$. The $ETCO_2$ was measured from within the endotracheal tube with a side-stream Engstrom Eliza CO_2 analyzer.

This work was presented in part at the American Society of Anesthesiologists 1991 Annual Meeting, October, San Francisco, California.

Accepted for publication February 28, 1992.

Address correspondence to Dr. Rich, University of Virginia Health Sciences Center, Department of Anesthesiology, Box 238, Charlottesville, VA 22908.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

After the control MAP and $ETco_2$ were recorded, a small balloon filled with 1% halothane and O_2 was attached to the breathing circuit, the system closed, and the rebreathing started. The $ETco_2$, respiratory frequency, and tidal volume were continuously recorded until the $ETco_2$ reached 9.5%. The breathing circuit was opened, and the rat was allowed to recover for 20 min. Ketorolac (0.2 mg/kg IV) or placebo was injected, and 20 min later the MAP, resting $ETco_2$, and CO_2 response curves were remeasured. The series was continued with IV ketorolac (2, 20, and 40 mg/kg) (n = 6) or IV placebo (n = 6). The MAP and $ETco_2$ after IV ketorolac injection were compared with control and placebo values by repeated measures analysis of variance (ANOVA). The slope of the CO_2 response curves between 7% and 9% $ETco_2$ and VE at 7%, 8%, and 9% $ETco_2$ were compared with control and placebo values by repeated measures ANOVA. The data are represented as mean values ± SEM and considered significant at $P < 0.05$.

Ventilation was controlled in six rats by means of a Harvard small-animal ventilator. The MAC was determined by measuring end-tidal halothane concentration (gas chromatography) at the time of application of a rubber-shod clamp to the tail (12). A positive response was gross body movement. The concentration of halothane was varied by 0.1%, allowing 12 min between changes to ensure steady-state conditions. The highest concentration at which the rat responded was averaged with the lowest concentration at which the rat did not respond for the value of MAC. After the MAC of halothane was determined, measurement of MAC was repeated 20 min after each of four successive doses of IV ketorolac (0.2, 2, 20, and 40 mg/kg). The MAC is presented as mean ± SEM and compared by repeated measures ANOVA.

Results

The baseline weight, temperature, pHa, $Paco_2$, Pao_2, heart rate, and MAP were not significantly different between rats receiving ketorolac or placebo (Table 1). Rectal temperature did not change significantly throughout the experiment in any of the groups. Ketorolac in doses up to 20 mg/kg IV did not significantly change MAP; however, 40 mg/kg produced a small but significant ($P < 0.05$) decrease in MAP compared with placebo (99 ± 8 versus 87 ± 6 mm Hg) (Figure 1).

The resting $ETco_2$ (5.1% ± 0.1%) did not change significantly with IV ketorolac compared with control or placebo values (Figure 2). The VE was calculated at an $ETco_2$ of 5.5%, 6.0%, 7.0%, 8.0%, 9.0%, and 9.5% in all rats with two exceptions (ketorolac 20 mg/kg; VE could not be calculated at 5.5% in two rats). The slope of the CO_2 response curve (70 ± 6 $mL \cdot min^{-1} \cdot \%^{-1}$) did not change after administration of IV ketorolac compared with control or placebo values (Figure 3). Likewise, comparison of VE between rats receiving placebo and ketorolac at an $ETco_2$ of 7%, 8%, and 9% (229 ± 17, 316 ± 15, and 371 ± 16 mL/min) revealed no significant differences. Statistically, there was a 95% chance of detecting a 0.2/5.1 (4%) change in

Table 1. Physiologic Data at Control Values for Both the CO_2 Response and Minimum Alveolar Anesthetic Concentration Studies

	CO_2 response		
	Placebo (n = 6)	Ketorolac (n = 6)	MAC (n = 6)
Wt (g)	313 ± 5	307 ± 7	311 ± 6
Temp (°C)	36.9 ± 0.1	36.8 ± 0.1	37.0 ± 0.1
pHa	7.39 ± 0.02	7.41 ± 0.02	7.42 ± 0.01
$Paco_2$ (mm Hg)	41.8 ± 1.3	42.4 ± 1.5	39.6 ± 0.6
Pao_2 (mm Hg)	215 ± 28	214 ± 23	*
HR (beats/min)	391 ± 5	388 ± 6	389 ± 3
MAP (mm Hg)	92 ± 5	95 ± 6	99 ± 4

HR, heart rate; MAP, mean arterial blood pressure; MAC, minimum alveolar anesthetic concentration.
* Controlled ventilation >300 mm Hg.

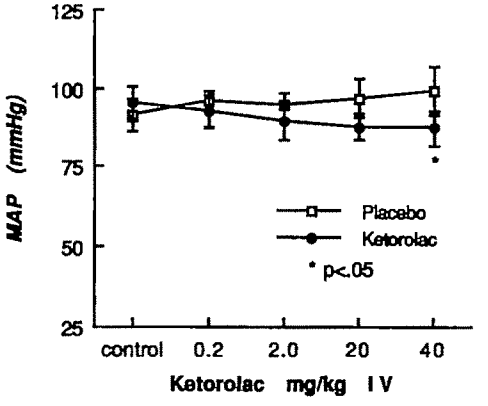


Figure 1. Mean arterial blood pressure (MAP) after ketorolac (n = 6) or placebo (n = 6) IV administration.

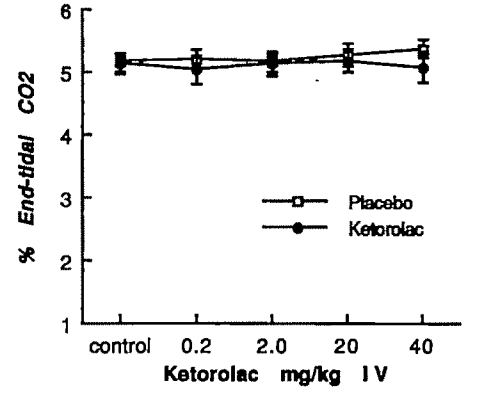


Figure 2. Resting $ETco_2$ after ketorolac (n = 6) or placebo (n = 6) IV administration.

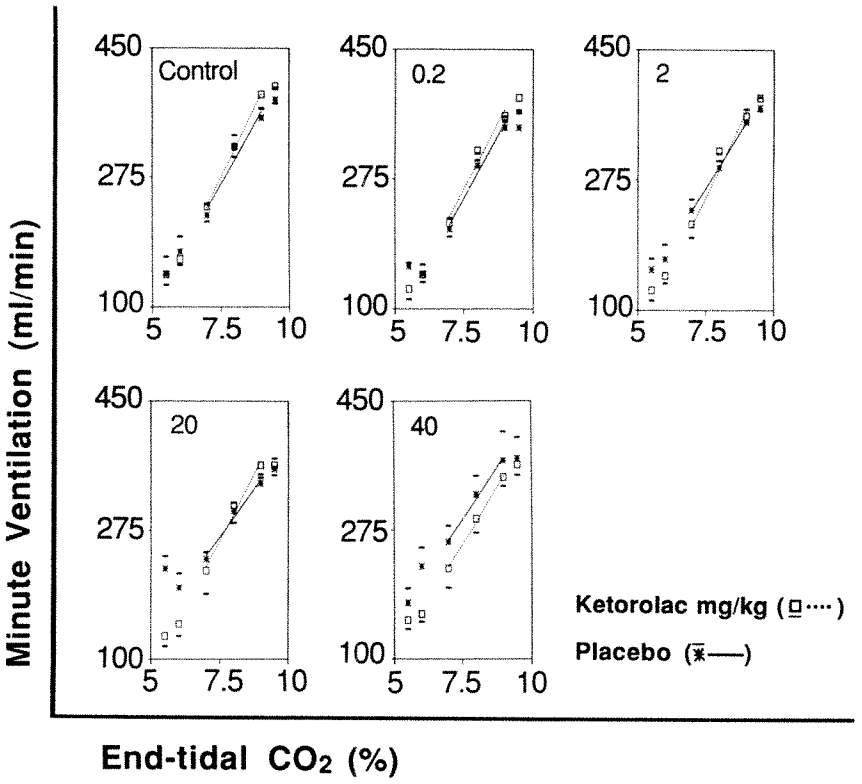


Figure 3. Mean values ± SEM of minute ventilation versus $ETCO_2$ after ketorolac (n = 6) or placebo (n = 6) IV administration.

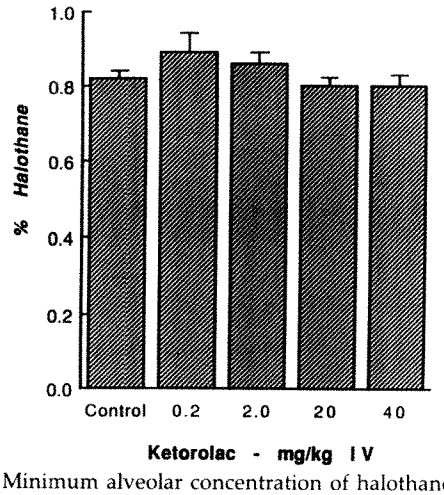


Figure 4. Minimum alveolar concentration of halothane (%) after ketorolac IV administration.

$ETCO_2$ and a 96% chance of detecting a 16% change in V_E. The MAC of halothane did not change significantly after administration of any of the four doses of IV ketorolac (Figure 4).

Discussion

Inflammatory pain and hyperalgesia may have two components resulting from prostaglandin release: a peripheral one, caused by the local sensitizing action of pain receptors, and a central one, possibly caused by the participation of central pain circuits (8). The nonsteroidal antiinflammatory drugs may exert analgesic action by preventing the hyperalgesia elicited by peripheral or central release of prostaglandins, or both (5–7).

In assays involving comparison of the yeast-inflamed paw in awake rats, oral ketorolac increased the pain threshold of the inflamed paw but not the noninflamed paw (9). This and the observation that oral ketorolac up to 49 mg/kg is inactive in the hot-plate test in awake mice (9) have suggested that ketorolac does not have central nervous system effects. It is unknown whether IV ketorolac in clinical or large doses has central nervous system effects that would decrease MAC or depress ventilation.

In rats, the minimal effective analgesic dose of oral ketorolac is 0.1–3.0 mg/kg, depending on the test for inhibition of pain (9). Human clinical doses required to produce analgesia are 0.5–1.5 mg/kg IV or IM (10,11). The smaller doses of ketorolac used in this study (0.2 and 2.0 mg/kg) bracket the clinical limits for both rats and humans. The larger doses (20 and 40 mg/kg) are one to two orders of magnitude larger than the effective dose. Because of the 5-h half-life of IV ketorolac (13), the final doses in this study were cumulative and therefore even larger than reported.

The MAC reduction was tested by means of the tail-clamp method, which is thought to detect MAC

changes due to central nervous system effects (14). In both clinical and large IV doses, there was no effect of ketorolac on the MAC of halothane in rats. This is consistent with previous studies (9) done with oral doses in awake mice and rats, that suggested that ketorolac, unlike the opioids, is an analgesic that lacks central nervous system effects.

Ventilatory depression secondary to IV ketorolac was determined by evaluation of resting $ETco_2$ and CO_2 response curves. The rats breathed 1% halothane and 99% oxygen, which minimizes peripheral chemoreceptor stimulation and allows evaluation of central nervous system respiratory effects. Ketorolac up to 90 mg does not produce respiratory depression in awake humans (10) and propofol-anesthetized patients (11). We demonstrated in this study that IV ketorolac does not depress ventilation. Because large IV doses do not affect resting $ETco_2$ or the slope of the CO_2 response curves, this further suggests that ketorolac lacks central nervous system effects.

Ketorolac in doses up to 30 mg IM (11) or 90 mg IV (15) does not change cardiac or hemodynamic variables in humans. In our study, only the large IV dose (40 mg/kg) was found to produce a statistically significant, but clinically modest, decrease in MAP. This suggests that ketorolac can be used with a large safety margin with respect to hemodynamic stability.

In conclusion, IV ketorolac in clinical and large doses does not decrease the MAC of halothane or cause depression of ventilation in rats. Furthermore, the lack of these effects in large doses suggests that ketorolac, unlike the opioids, does not have a central nervous system mechanism of action.

References

1. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine sparing effect of ketorolac tromethamine. Pediatrics 1975;55:727–31.
2. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556–61.
3. Estenne B, Julien M, Charleux H, Arsac M, Arvis G, Loygue J. Comparison of ketorolac, pentazocine, and placebo in treating postoperative pain. Curr Ther Res 1988;43:1173–82.
4. Yee JP, Koshiver JE, Allbon C, Brown CR. Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Pharmacotherapy 1986;6:253–61.
5. Okuyama S, Aihara H. The mode of action of analgesic drugs in adjuvant arthritic rats as an experimental model of chronic inflammatory pain: possible central analgesic action of acidic nonsteroidal antiinflammatory drugs. Jpn J Pharmacol 1984;35:95–103.
6. Ferreira SH, Lorenzetti BB, Correa FMA. Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 1978;53:39–48.
7. Torebjork HE, Schady W, Ochoa JL. A new method for demonstration of central effects of analgesic agents in man. J Neurol Neurosurg Psychiatry 1984;47:862–9.
8. Zoppi M, Zamponi A. Anti-inflammatory drugs. Adv Pain Res Ther 1990;13:329–35.
9. Rooks WH II, Maloney PJ, Shott LD, Schuler ME, Sevelius H. The analgesic and anti-inflammatory profile of ketorolac and its tromethamine salt. Drugs Exp Clin Res 1985;11:479–92.
10. Brandon Bravo LJC, Mattie H, Spierdijk J, Bovill JG, Burm AGL. The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 1988;35:491–4.
11. Murray AW, Brockway MS, Kenny GNC. Comparison of the cardiorespiratory effects of ketorolac and alfentanil during propofol anaesthesia. Br J Anaesth 1989;63:601–3.
12. Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS. The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. Anesth Analg 1983;62:987–90.
13. Jung D, Mroszczak E, Byrum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol 1988;35:423–5.
14. Eger EI, II, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965;26:756–63.
15. Camu F, Van Overberghe L, Bullingham R, Lloyd J. Hemodynamic effects of ketorolac tromethamine in comparison to morphine in anesthetised patients. Proceedings of the Ninth World Congress of Anesthesiologists, 1988:A0167.

Effect of Chloride Transport Blockade on the MAC of Halothane in the Rat

George F. Rich, MD, PhD, Maryrose P. Sullivan, PhD, and J. Milton Adams, PhD

Departments of Anesthesiology and Biomedical Engineering, University of Virginia Health Sciences Center, Charlottesville, Virginia

There is growing evidence that central nervous system chloride transport via γ-aminobutyric acid ($GABA_A$) related Cl^- conductance or Cl^-/HCO_3^- exchange affects anesthetic requirements. To delineate the effects of $GABA_A$-related Cl^- conductance blockade versus Cl^-/HCO_3^- exchange inhibition, we determined the change in minimum alveolar anesthetic concentration (MAC) of halothane in rats after intracisternal infusion of 4,4'-diisothiocyano-2,2'-disulfonic acid stilbene (DIDS). DIDS inhibits Cl^-/HCO_3^- exchange transport in concentrations >1 μM and in $GABA_A$-related Cl^- channels in concentrations >0.1 mM. After control MAC determination, rats were given intracisternal mock cerebrospinal fluid (n = 6), 1.0 μM DIDS (n = 8), or 1 mM DIDS (n = 8) at a rate of 2 μL/min for 30 min. Mock cerebrospinal fluid did not change the MAC of halothane. The MAC of halothane increased significantly ($P < 0.001$) from 0.96% ± 0.02% to 1.11% ± 0.03% (mean value ± SEM) with 1 μM DIDS and from 0.94% ± 0.02% to 1.16% ± 0.04% with 1 mM DIDS. The increases in MAC with 1 μM and 1 mM DIDS were not statistically different. This suggests that Cl^-/HCO_3^- exchange inhibition increases halothane requirements, whereas $GABA_A$-related Cl^- channel blockade does not.

(Anesth Analg 1992;75:103–6)

The mechanisms of action of general anesthetics remain largely speculative; however, there is increasing evidence that anesthetics enhance inhibitory transmission within the central nervous system, with γ-aminobutyric acid (GABA) acting as an inhibitory transmitter (1–7). The $GABA_A$ complex consists of receptors for benzodiazepines, barbiturates, and an associated Cl^- channel (8). Activation of Cl^- channels by GABA allows Cl^- to enter the cell and hyperpolarize the membrane. Barbiturates, benzodiazepines, and, possibly, volatile anesthetics enhance the actions of GABA and inhibitory postsynaptic potentials by increasing Cl^- conductance. (9–12).

Recently, Matsumura et al. (13) demonstrated that antagonism of Cl^- transport with L-644,711 increases the minimum alveolar anesthetic concentration (MAC) of isoflurane in rats. L-644,711 inhibits Cl^-/HCO_3^- exchange and glutamate uptake; however, its effect on $GABA_A$-related Cl^- channels is unknown (14). To examine further the effects of Cl^- transport blockade on MAC, we administered intracisternal 4,4'-diisothiocyano-2,2'-disulfonic acid stilbene (DIDS) to halothane-anesthetized rats. In concentrations >1 μM, DIDS inhibits Cl^-/HCO_3^- exchange, whereas in concentrations >0.1 mM, DIDS antagonizes the $GABA_A$-associated Cl^- channel (15–21). If volatile anesthetics are mediated by GABA-related increases in synaptic inhibition, we hypothesized that Cl^- channel blockade resulting from high-dose DIDS would result in an increase in MAC. On the other hand, if Cl^-/HCO_3^- exchange affects anesthesia, then lower as well as higher concentrations of DIDS should increase MAC.

Methods

This study was approved by the University of Virginia Animal Research Committee. Twenty-two Sprague-Dawley rats weighing 260–340 g were anesthetized in a plastic chamber with halothane and O_2. A 14-gauge catheter was inserted into the trachea by means of a tracheostomy and was attached to a Mapleson D circuit, allowing spontaneous ventilation. The right femoral artery was cannulated to monitor arterial blood pressure and heart rate by a pressure transducer and Hewlett-Packard recorder and to allow blood gas analysis. The rats were placed in a stereotactic head frame with ear pins and posi-

Accepted for publication February 28, 1992.

Address correspondence to Dr. Rich, University of Virginia Health Sciences Center, Department of Anesthesiology, Box 238, Charlottesville, VA 22908.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

tioned on a plastic support heated by a thermostatic water bath designed to maintain the rats at normothermia. A 24-gauge Teflon catheter was inserted through the atlanto-occipital membrane and into the cisterna magna, allowing infusion of cerebrospinal fluid (CSF).

A CSF perfusion system infused mock CSF with and without DIDS through the 24-gauge catheter and into the cisterna magna. The system consisted of a syringe pump and heat exchanger designed so that the perfusate was brought to 37°C before it passed into the cisterna magna. Mock CSF solution was made as a sterile solution of electrolytes with the following concentrations (mM): 143 Na^+, 3.6 K^+, 1.53 Ca^{2+}, 1.20 Mg^{2+}, 126 Cl^-, 0.13 H_2PO_4, and 22.6 HCO_3^- and glucose (10 mM). Mock CSF was bubbled with 95% O_2–5% CO_2 and titrated to pH 7.34 with HCl at 37°C; DIDS at concentrations of 1 μM or 1 mM was added to the mock CSF.

The rats were divided into three groups. In six rats, control MAC was determined, followed by infusion of mock CSF at a rate of 2 μL/min. Thirty minutes later, MAC was again determined. The same procedure was repeated before and after infusion of mock CSF containing 1 μM DIDS (n = 8) and 1 mM DIDS (n = 8). The halothane concentration was measured by infrared analysis (Beckman LB2) sampled from the midpoint of the endotracheal tube. The MAC was determined by measuring end-tidal halothane concentration at the time of application of a rubber-shod tubing clamp to the base of the tail. A positive response was movement of a leg or foot. The concentration of halothane was varied 0.1%, allowing 10 min between changes to ensure steady-state conditions. The highest concentration at which the rat responded was averaged with the lowest concentration at which the rat did not respond for the value of the MAC. Statistical analysis was by repeated measures analysis of variance (ANOVA), followed by Neuman Keuls test (SYSTAT). Data are presented as mean values ± SEM.

Results

The control MAC of halothane for the 22 rats before CSF infusion was 0.95% ± 0.03% and was not statistically different among the three groups. The MAC of halothane did not change in the six rats infused with mock CSF (Figure 1). Infusion of 1 μM DIDS significantly ($P < 0.001$) increased the MAC of halothane from 0.96% ± 0.02% to 1.11% ± 0.03%. Similarly, infusion of 1 mM DIDS significantly ($P < 0.001$) increased the MAC of halothane from 0.94% ± 0.02% to 1.16% ± 0.04%. There was no significant difference in MAC between groups receiving infusion of 1 μM and 1 mM DIDS.

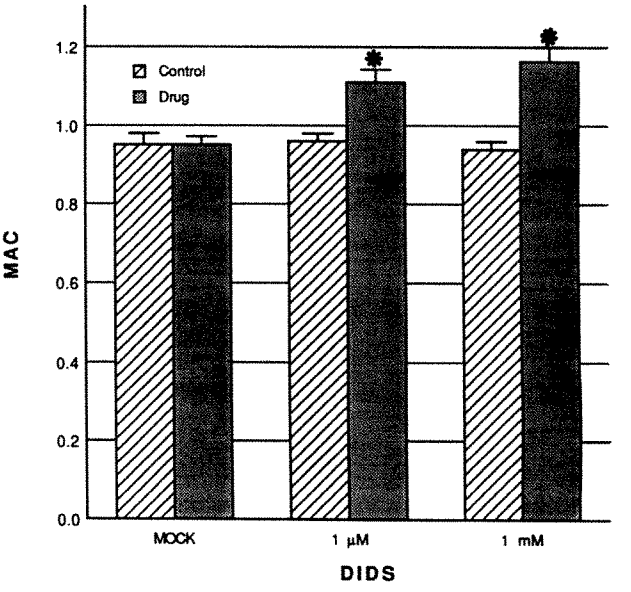


Figure 1. Minimum alveolar anesthetic concentration (MAC) of halothane with and without DIDS (mean value ± SEM). *Significantly ($P < 0.001$) different from control, but not from each other. MOCK, mock cerebrospinal fluid.

Blood gas analysis before CSF infusion revealed a Pa_{O_2}, Pa_{CO_2}, and pHa of 311 ± 9 mm Hg, 42 ± 3 mm Hg, and 7.37 ± 0.02, respectively. Mean arterial blood pressure and heart rate were 82 ± 4 mm Hg and 342 ± 15 beats/min, respectively. The temperature was maintained at 37.3 ± 0.1°C. There was no difference among the three groups with regard to these variables.

Discussion

Halothane, isoflurane, and enflurane all augment GABA-induced ionic currents in vitro. This suggests that their action is in part related to GABA inhibition (1–7). Benzodiazepines and barbiturates decrease the MAC of volatile anesthetics, probably by increased $GABA_A$-related Cl^- conductance (9–12). Conversely, antagonism of the benzodiazepine/barbiturate/$GABA_A/Cl^-$ channel complex has demonstrated mixed results. In vitro blockade of Cl^- channel activation with bicuculline inhibits synaptic transmission (8). Similarly, in vitro administration of DIDS in concentrations >0.1 mM reverses the effects of benzodiazepines (21). Recent in vivo studies (22–24) with intravenous flumazenil, a benzodiazepine antagonist, have indicated unchanged or decreased MAC of volatile anesthetics. Matsumura et al. (13) recently demonstrated that intracisternal infusion of L-644,711 increases the MAC of isoflurane in rats. L-644,711 inhibits Cl^-/HCO_3^- exchange and glutamate uptake,

but its effects on the $GABA_A$-related Cl^- channels are unknown. Further, it is not clear whether L-644,711 inhibits Cl^-/HCO_3^- exchange or glutamate uptake, or both, in these experiments. Thus, conclusions concerning the mechanisms of action of volatile anesthetics and their relationship to $GABA_A$-related Cl^- conductance and Cl^-/HCO_3- exchange have been inconclusive. We postulated that if volatile anesthetic actions involved GABA, then only high-dose DIDS, which inhibits $GABA_A$-related Cl^- conductance, would increase MAC. Conversely, if Cl^-/HCO_3^- exchange affects anesthesia, then both low and high doses of DIDS should increase MAC.

Disulfonic stilbene derivatives, DIDS and 4-acetamido-4′-isothiocyano-2,2′-disulfonic acid stilbene (SITS), block two types of anion transport across cell membranes. Voltage- or ligand-gated channels can open or close and contribute to membrane conductance, whereas exchange (i.e., Cl^-/HCO_3^- exchange) is not gated, nor is it electrogenic. DIDS inhibits anion exchange with a K_i (concentration that produces 50% inhibition) of 1.2–2 μM; the K_i for SITS is higher at 25 μM (15,16). The inhibition of anion channels appears to occur at higher concentrations. SITS depresses GABA-induced depolarization in cat dorsal root ganglia at 200 μM, achieving approximately 50% inhibition at 1 mM (17), indicating a much higher K_i. GABA-dependent Cl^- uptake into mouse brain membranes is not affected by SITS until 30 μM (18). Chlorine ion-dependent glutamate uptake by brain membranes is depressed by higher concentrations of SITS and DIDS (19,20). GABA-dependent benzodiazepine binding to rat brain homogenate is also inhibited by higher concentrations of DIDS (21).

It is not known whether the protein binding domains for inhibitors are the same for anion channels and exchangers or whether the kinetics are the same or if they differ among cell types. No studies have shown significant inhibition of channel activity at 1 μM concentration but have for Cl^-/HCO_3^- exchange. Therefore, it is most likely that the increased MAC for halothane at 1 μM DIDS is due to blocking Cl^-/HCO_3^- exchange, not Cl^- channel-related events. If DIDS inhibits $GABA_A$-related Cl^- channels or other anion channel-related activity, it should be fully evident at 1 mM, yet we saw no significant increase in MAC above the 1 μM concentration. This evidence suggests that DIDS inhibition of $GABA_A$-related Cl^- channels was not responsible for the increased MAC of halothane, because the effects of Cl^-/HCO_3^- exchange inhibition were fully evident at 1 μM, and no further increase occurred at a 1000-fold higher concentration.

The Cl^-/HCO_3^- exchange has a role in the cellular maintenance of pH and volume. It is possible that the inhibition of exchange could affect MAC through these general mechanisms. It is also possible that Cl^-/HCO_3^- exchange inhibition could indirectly affect channel-related Cl^- movement as a pathway in the overall movement of Cl^-. In other words, Cl^- that entered the cell through a channel may need to leave through an exchanger.

We attempted to maximize brain concentration and minimize systemic effects by administering DIDS intracisternally. Although we cannot document central nervous system concentrations of DIDS, intracisternally injected blue dye produces diffuse staining (25). It is unlikely that DIDS increases MAC by generalized stimulant effects or catecholamine release, because intracisternal DIDS does not produce hemodynamic changes (25). In this study, DIDS increased the MAC of halothane by 16%–23%, whereas Matsumura et al. (13) showed a 63% increase in isoflurane MAC with L-644,711. Both DIDS and L-644,711 produced significant effects on anesthetic requirement in similar rat models. It is not known whether the difference in anesthetics (halothane versus isoflurane), the potency of the inhibitors, or the significant systemic effects of L-644,711 could account for the difference. Nevertheless, both studies demonstrate that antagonism of Cl^- transport affects anesthetic requirements. Our study indicates that this is probably secondary to Cl^-/HCO_3^- exchange inhibition.

In conclusion, halothane anesthetic requirements were significantly increased in rats given intracisternal DIDS. This supports previous evidence that volatile anesthetic actions may in part be mediated by Cl^- transport. The mechanism for the MAC increase, however, appears to be the inhibition of the Cl^-/HCO_3^- exchange rather than the blockade of $GABA_A$-related Cl^- channels.

References

1. Nakahiro M, Yeh JZ, Brunner E, Narahashi T. General anesthetics modulate GABA receptor channel complex in rat dorsal root ganglion neurons. FASEB J 1989;3:1850–4.
2. Nicoll RA. The effects of anaesthetics on synaptic activation and inhibition in olfactory bulb. J Physiol (Lond) 1972;223:803–14.
3. Scholfield CN. Potentiation of inhibition by general anaesthetics in neurones of the olfactory cortex in vitro. Pfluegers Arch 1980;383:249–55.
4. Lodge D, Anis NA. Effects of ketamine and three other anaesthetics on spinal reflexes and inhibitions in the cat. Br J Anaesth 1984;56:1143–51.
5. Gage PW, Robertson B. Prolongation of inhibitory postsynaptic currents by pentobarbitone, halothane and ketamine in CA1 pyramidal cells in rat hippocampus. Br J Pharmacol 1985;85:675–81.
6. Lalley PM. Inhibition of depressor cardiovascular reflexes by a derivative of γ-aminobutyric (GABA) and by general anesthetics with suspected GABA-mimetic effects. J Pharmacol Exp Ther 1980;215:418–25.

7. Keane PE, Biziere K. The effects of general anesthetics on GABAergic synaptic transmission. Life Sci 1987;41:1437–48.
8. Bormann J. Electrophysiology of $GABA_A$ and $GABA_B$ receptor subtypes. Trend Neurosci 1988;11:112–6.
9. Barker JL, Ransom BR. Pentobarbitone pharmacology of mammalian central neurones grown in tissue culture. J Physiol (Lond) 1978;280:355–72.
10. Melvin MA, Brynte HJ, Quesha AL, Eger EL. Induction of anesthesia with midazolam decreases halothane MAC in humans. Anesthesiology 1982;57:238–41.
11. Brown DA, Constanti A. Interaction of pentobarbitone and γ-aminobutyric acid on mammalian sympathetic ganglion cells. Br J Pharmacol 1978;63:217–24.
12. MacDonald RL, Barker JL. Enhancement of GABA-mediated postsynaptic inhibition in cultured mammalian spinal cord neurons: a common mode of anticonvulsant action. Brain Res 1979;167:323–36.
13. Matsumura JS, Cole DJ, Schjell RM, Wong MH. L-644,711, a novel anion transport inhibitor, increases isoflurane MAC in rats. Anesth Analg 1991;73:199–203.
14. Kimelberg HK, Rose JW, Barron DK, Waniewski RA, Cragoe EJ. Astrocytic swelling in traumatic-hypoxic brain injury. Mol Chem Neuropathol 1989;11:1–31.
15. Cabantchik ZI, Knauf PA, Rothstein A. The axion transport system of the red blood cell. The role of membrane protein evaluated by the use of "probes." Biochem Biophys Acta 1978;515:239–303.
16. Eidelman O, Yanai P, Englert HC, Lang HG, Greger R, Cabantchik ZI. Macromolecular conjugates of transport inhibitors: new tools for probing topography of anion transport proteins. Am J Physiol 1991;260:C1094–103.
17. Gallagher JP, Nakamura J, Shinnick-Gallagher P. The effects of temperature, pH and Cl^- pump inhibitors on GABA responses recorded from cat dorsal root ganglia. Brain Res 1983;267:249–59.
18. Allan AM, Harris RA. γ-Aminobutyric acid agonists and antagonists after chloride flux across brain membranes. Mol Pharmacol 1986;29:497–505.
19. Waniewski RS, Martin DL. Selective inhibition of glial versus neuronal uptake of l-glutamine acid by SITS. Brain Res 1983; 268:390–4.
20. Recasens M, Pin JP, Bockaert J. Chloride transport blockers inhibit the chloride-dependent glutamate binding to rat membranes. Neurosci Lett 1987;74:211–6.
21. Costa T, Russell L. Pert CB, Rodbard D. Halide- and γ-aminobutyric acid-induced enhancement of diazepam receptors in rat brain. Mol Pharmaco 1981;20:470–6.
22. Schwartz AE, Maneksha FR, Kanchuger MS, Sidhu US, Poppers JP. Flumazenil decreases the minimum alveolar concentration of isoflurane in dogs. Anesthesiology 1989;70:764–6.
23. Schwieger IM, Szlam F, Hug CC. Absence of agonistic or antagonistic effect of flumazenil (Ro 15-1788) in dogs anesthetized with enflurance, isoflurance, or fentanyl-enflurane. Anesthesiology 1989;70:477–80.
24. Greiner AS, Larach DR. The effect of benzodiazepine receptor antagonism by flumazenil on the MAC of halothane in the rat. Anesthesiology 1989;70:644–8.
25. Adams JM, Johnson NL. Intracisternal DIDS enhances ventilatory response to rebreathing CO_2 in rats. J Appl Physiol 1988;65:1611–6.

Isoflurane Anesthesia Prevents Unconscious Learning

R. Dwyer, FFARCSI, H. L. Bennett, PhD, E. I. Eger II, MD, and N. Peterson, BS

Departments of Anesthesiology, University of California, School of Medicine, San Francisco and Davis, California and Department of Anaesthesia, Beaumont Hospital, Dublin, Ireland

We investigated whether ≥0.6 minimum alveolar concentration (MAC) of isoflurane suppresses learning of information presented verbally. Preoperatively, we asked 45 healthy patients (aged 23–58 yr) undergoing elective surgery 15 general knowledge questions designed to arouse their curiosity. They were told that they would be given the answers during anesthesia. Anesthesia was induced with isoflurane and nitrous oxide (25 subjects also received 1.1 ± 0.6 mg/kg of propofol). The trachea was intubated with the aid of vecuronium (0.07 mg/kg IV). Isoflurane in oxygen was given to provide 0.6 MAC before and 1.0 and 1.4 MAC during surgery. After 10 min at each of two of the three MAC levels, the answers were given to five of the questions. At the remaining concentration, patients received a message to either touch an ear (n = 30) or keep their arms still (n = 15) during the postoperative interview. Twenty-four hours later, patients were asked whether they recalled intraoperative events. They were then asked to answer the 15 questions, choosing from five possible answers to each, one of which was correct. The number of times each patient touched an ear during this interview was noted. No patient consciously recalled events during anesthesia. The number of questions answered correctly postoperatively did not differ according to whether the answers had been provided during anesthesia (at any isoflurane concentration) or had not been provided (control questions). The number of ear-touches postoperatively did not differ between those who had and had not received the intraoperative message encouraging ear-touching. Our results suggest that isoflurane concentrations of ≥0.6 MAC prevent conscious recall and unconscious learning of factual information and behavioral suggestions.

(Anesth Analg 1992;75:107–12)

Conscious recall of events during anesthesia, although rare (1,2), may be extremely unpleasant (3,4) but is prevented by relatively small concentrations of volatile anesthetics (5–9). There is, however, considerable evidence that patients may retain or "learn" information communicated during anesthesia without conscious recall of having received such information (10–18); but other methodologically similar studies have failed to demonstrate learning during anesthesia (19–24).

Many studies demonstrating learning without conscious recall have not controlled the depth of anesthesia (as defined by end-tidal anesthetic concentration), and we do not know whether anesthesia was adequate at the times that learning occurred. Although increased concentrations of anesthetics decrease awareness (5–8), the effect of anesthetic dose or "depth of anesthesia" on unconscious learning is unclear, and it has been suggested that intraoperative unconscious learning may occur independently of anesthetic depth (18). Similarly, many of the studies demonstrating learning during anesthesia did not use a standardized anesthetic technique. The effect of different anesthetic agents on unconscious learning is unknown, and differences in results among various studies and subjects could be explained by differences in anesthetic doses and agents.

Recent work on memory has differentiated between explicit and implicit memory and shown that information requiring implicit (unconscious) rather than explicit (conscious) memory is more readily retained in amnesic states (25,26). Most studies showing learning during anesthesia used tests of implicit memory, suggesting that implicit learning may occur during anesthesia despite the abolition of explicit memory (27).

To determine whether intraoperative learning occurs during adequate isoflurane anesthesia and

This work was presented in part at the International Anesthesia Research Society Annual Meeting, San Antonio, Texas, March 1991.

This work was supported in part by Anaquest Inc.

Accepted for publication February 28, 1992.

Address correspondence to Dr. Eger, Department of Anesthesiology, University of California, San Francisco, Box 0648, Room S455, 531 Parnassus Avenue, San Francisco, CA 94143-0648.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

whether increasing concentrations of isoflurane decrease intraoperative learning, we measured intraoperative learning of factual information and assessed the effect of intraoperative suggestion on postoperative behavior in patients undergoing elective surgery. We used tests of implicit memory to examine the effect of learned information on later behavior and performance without requiring conscious recall of the learned material.

Methods

We studied 45 healthy subjects, aged 23–58 yr, scheduled for elective surgery that permitted participation in an interview on the first postoperative day. All gave informed consent, and the study was approved by our institutional Committee on Human Research.

Patients were interviewed 1 day before surgery, according to a standardized format. The background and aims of the study were presented in order to prepare the patients for the verbal material to be presented during anesthesia and to motivate them to "learn" as much as possible of the material. Each patient was asked 15 general knowledge questions that were designed to be interesting but so obscure that the answers were unlikely to be known (e.g., "which U.S. state has a leash law for elephants?"). Answers to the questions were noted. Patients were told that the answers would be presented during anesthesia and were asked to remember the answers. In addition, each was told that he or she would hear a research message, the nature of which was unspecified, that should be remembered. The number of times each subject touched either ear during the interview was noted without mentioning this observation to the subject.

Patients were given no premedication before transfer to the operating room. Anesthesia was induced by inhalation of isoflurane in N_2O and O_2, supplemented if necessary for smooth induction by a small dose of propofol (1.1 ± 0.6 mg/kg) (mean dose ± SD) (n = 25). Endotracheal intubation was facilitated by administration of vecuronium (0.07 mg/kg IV). Positive-pressure ventilation was adjusted to maintain normocarbia. Nitrous oxide was eliminated by fresh gas inflows of 5 L/min, and anesthesia was provided by isoflurane alone, the inspired concentration adjusted to maintain the end-tidal concentration at 0.6 MAC (adjusted for age). When the patient was positioned for surgery, a set of headphones that excluded room noise was placed over the patient's ears, and a tape of the sound of a running stream was played through the headphones, except during presentation of information. After a minimum of 15 min without N_2O and 10 min at 0.6 MAC end-tidal isoflurane concentration, patients heard taped messages (see later) through the headphones.

The inspired isoflurane concentration was increased and surgery began. During surgery, patients heard additional messages after equilibration for 10 min each at end-tidal isoflurane concentrations of 1.0 and 1.4 MAC (order randomized). At two of the three end-tidal isoflurane concentrations (randomly selected), the messages consisted of answers to five of the general knowledge questions, with both the questions and answers repeated three times. At the remaining end-tidal concentration, patients were told either to touch an ear during the postoperative interview (n = 30, equally distributed to the three end-tidal isoflurane concentrations) or to keep their arms still during the interview (n = 15). Both behavioral messages added that recovery would be rapid and comfortable. The taped messages were monitored to ensure full delivery of all information to the patient. Messages were played at a normal listening volume, as judged by the researcher.

After completion of presentation of all messages, the clinician supplemented anesthesia with N_2O or narcotics, or both, as clinically indicated. Postoperative analgesia was provided by either parenteral or epidural narcotics, according to the usual protocols of our institution.

On the day after surgery, all patients were asked whether they had any conscious memory of surgery or intraoperative messages. Patients were shown the 15 preoperative questions (in a written, multiple-choice format, with five possible answers to each question) and were asked to mark the answer they thought correct. The number of times patients touched an ear during the interview was noted by a second observer unaware of which behavioral message had been presented during anesthesia.

To demonstrate that this material was easily learned and retained despite anesthesia and surgery, we analyzed the results from a control group of 24 additional patients who were interviewed on the day before surgery with the same format used in the study group. The control subjects received the answers to 10 questions before rather than during anesthesia. On the day after surgery, they were asked to choose the correct answers (multiple-choice format) to each of the 15 questions.

The number of correct answers was compared between answers presented at each dose of isoflurane and control answers that had not been presented using a paired t-test. The Mann-Whitney U-test was used to compare the number of ear-touches during the postoperative interview between patients who did versus those who did not receive an intraoperative message to touch an ear. A P value of <0.05 was considered statistically significant.

Table 1. Clinical Characteristics and Duration of Anesthesia in the Control and Study Groups

	Control group (n = 24)	Study group (n = 45)
Age (yr)	40 ± 10	39 ± 9
Weight (kg)	73 ± 15	74 ± 14
Male/female (n)	10/14	19/26
Duration of anesthesia (min)	190 ± 60	204 ± 110

Values are mean ± SD.

Table 2. Learning in the Control and Study Groups

	Control group (n = 24)	Study group (n = 45)
Presented answers	97.9% ± 4.1%	22.2% ± 15.5%
Nonpresented answers	14.2% ± 19.1%	22.2% ± 19.6%

Numbers given are percent of answers correct (mean values ± SD).

Results

Patient age and weight and the duration of anesthesia did not differ significantly between study and control patients (Table 1). No patient consciously recalled intraoperative events.

Control subjects remembered almost all of the answers provided preoperatively. The percent correct of the 10 answers presented preoperatively greatly exceeded correct answers to the 5 control questions (i.e., nonpresented answers) (Table 2).

The percent of questions answered correctly preoperatively by the study subjects (without benefit of five multiple-choice answers to choose from) was 7.7% ± 5.3% (mean value ± SD). These questions were included in further analyses. The percent of answers correct postoperatively did not differ significantly between answers presented during anesthesia and control (nonpresented) answers (Table 2, Figure 1). The anesthetic concentration at which answers were presented did not influence the number of correct answers during the postoperative interview (Figure 1). Numbers of answers correct followed similar distributions for answers presented at each anesthetic concentration and for control questions (nonpresented answers); i.e., there were no outliers to suggest an idiosyncratic level of learning in certain individuals.

Six patients were interviewed without a second observer to count ear-touching. Although ear-touches were counted in these patients, they were excluded from analysis of the ear-touching response to ensure reliability of this measurement. Of the remaining 39 patients, 44% receiving an intraoperative ear-touching message touched their ear during the interview, compared with 43% of the control group. The number of times an ear was touched during the pre- and postoperative interviews did not differ between patients who received an intraoperative ear-touching message and control patients (Table 3). Similarly, an increase in ear-touching from the pre- to postoperative interview was noted in 32% of the study group and in 36% of the control group. Comparison of postoperative ear-touching between patients who received the ear-touching message at the lowest end-tidal isoflurane concentration (0.6 MAC) and control patients revealed no effect of the message on ear-touching behavior. Inclusion of ear-touching data from the six patients in whom it was counted by the interviewer made no difference to these findings.

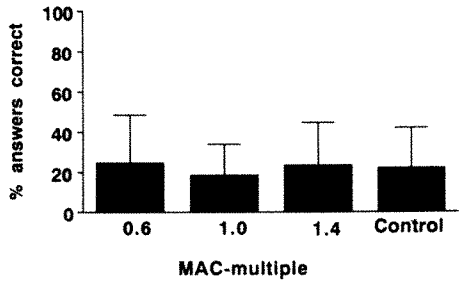


Figure 1. The percent of answers correct after anesthesia did not differ between answers presented at any of the three concentrations of isoflurane and control group answers that had not been presented (mean values ± SD). MAC, minimum alveolar anesthetic concentration.

Table 3. Effect of a Behavioral Message During Anesthesia

Ear-touching	Study group (ear-touching message) (n = 25)	Control group (n = 14)
Preoperative	0 (0–0)	0 (0–1)
Postoperative	0 (0–1)	0 (0–4)
Increased	32%	36%
Decreased	8%	21%

An ear-touching message during anesthesia did not alter the number of ear-touches that occurred during the postoperative interview (median, quartiles) or the percent of patients in whom ear-touching increased or decreased between the pre- and postoperative interviews.

Discussion

We found no evidence of unconscious learning of factual information during isoflurane anesthesia at doses typical of those used in clinical practice despite choosing a task that has previously been used to demonstrate unconscious learning during anesthesia (13). Isoflurane at end-tidal concentrations of ≥0.6 MAC prevented either retention in memory or later retrieval of this type of information.

Although some studies have shown that intraoperative suggestion can elicit a particular motor behavior (12,14), this has not been a universal finding (24). Our data suggest that concentrations of ≥0.6 MAC isoflurane abolish the ability of intraoperative suggestion to cause a specific postoperative behavior (ear-touching). It should be noted that information was presented at 0.6 MAC isoflurane in the absence of surgical stimulation, and it is possible that the arousing effect of surgical stimulation might increase the anesthetic concentration required to prevent learning.

Two factors in our protocol may have confounded our results. We gave propofol for induction of anesthesia to 56% of our patients. This may have affected retention of material presented at 0.6 MAC, which we tested first; however, we believe any such effect was small because we began presentation of auditory information at least 20 min after propofol administration and because the dose of propofol was small (about half of that commonly used for induction of anesthesia). Our belief is strengthened by the absence of a significant difference in the percent of answers correct after presentation at 0.6 MAC between patients given propofol (22.5% ± 21.8%, n = 16) and patients not given propofol (27.1% ± 26.7%, n = 14) (mean values ± SD).

Similarly, N_2O was used for induction of anesthesia in all patients, and its residual effects may have potentiated the depressant effects of isoflurane on learning; however, we discontinued administration of N_2O for a minimum of 15 min before the presentation of information. At the time of presentation of information, the end-tidal concentration of N_2O was <5% in all patients and usually much lower, with a mean (±SD) end-tidal N_2O concentration of 2.4% ± 0.6%. Ten minutes before presentation of information, the mean end-tidal concentration of N_2O was 8.3% ± 3.5%, indicating that low levels had been present for a period sufficient to have eliminated most of the N_2O from the brain.

Many previous studies that demonstrated intraoperative learning used N_2O as a component of anesthesia (10–12,15–17). Nitrous oxide alone does not reliably prevent conscious awareness during anesthesia (7,8,28,29). In addition, tolerance to its effects may develop (30–32). Nitrous oxide has some characteristics of a central nervous system stimulant (33–35). It fails to supplement isoflurane-induced depression of cerebral metabolic rate (36) and may antagonize the electroencephalographic effects of volatile agents (37). Perhaps N_2O also has the capacity to antagonize the ability of potent volatile agents to impair learning. It has an additive effect with the volatile agents in preventing movement in response to surgical incision (38); however, this may not translate to additivity for suppression of learning during anesthesia. We maintained anesthesia with only isoflurane, without relying on N_2O—perhaps this explains the difference in our results from other investigators who used N_2O.

Several other reasons may explain the difference between our results and those of previous investigators. Most previous studies did not measure and control the end-tidal concentrations of inhaled anesthetics. Thus, subjects in previous studies may have experienced learning because of inadequate doses of anesthetic agents.

Our study was designed to optimize conditions for revealing implicit learning: (a) questions were chosen because they were likely to arouse the patients' interest; (b) patients were asked questions preoperatively to prime them to "hear" the answers intraoperatively; (c) benzodiazepines were not administered perioperatively; and (d) patients were provided with a list of five possible answers (one of which was correct) to prompt memory. The results from the control subjects who were given the answers before surgery while still conscious showed almost complete learning of the material presented before anesthesia, demonstrating that this material was easily learned and retained despite subsequent anesthesia and surgery. Nevertheless, the learning task used in our study required some cognitive processing before retention in memory. Two recent studies (18,39) that demonstrated learning during adequate anesthesia (as indicated by end-tidal concentrations) used tests of implicit memory (word association, word completion, and word preference) that required less cognitive processing than the task used in our study. Thus, isoflurane may prevent learning that requires some cognitive processing, as in our study, but may permit learning of single words after multiple repetitions, which probably requires minimal cognitive processing. However, this does not explain the difference between the study of Block et al. (18) and ours as to the effect of an intraoperative behavioral message on postoperative motor behavior.

Block et al. (18) found a positive correlation between the number of repetitions of nonsense words and a later preference for and recognition of these words, suggesting that frequent repetition of information during anesthesia may increase implicit learning during anesthesia. It is possible that more repetition of the material presented in our study would have allowed statistically significant learning to occur. However, if learning occurs during isoflurane anesthesia only when the information has minimal factual content and requires multiple repetition, this

suggests that the phenomenon may have little clinical significance.

Our results are consistent with the possibility that a few, but not all, of our subjects learned during anesthesia. A few such "sensitive" subjects would suggest the possibility of a bimodal distribution of correct answers, but this was not found; however, one patient identified 7 of 10 correct answers for questions answered during anesthesia and 0 of 5 for control questions ($P < 0.06$, Fisher's two-tailed exact test). Although this may have occurred by chance, it raises the question of whether patients differ in their capacity to learn during anesthesia and whether a few particularly "sensitive" patients are responsible for some isolated reports of awareness during anesthesia. If learning does occur, its demonstration will require either a more sensitive task or testing of greater numbers of subjects. Additionally, if learning does occur during isoflurane anesthesia, it may be attributed to the effect of a small number of subjects in the group who learned rather than an effect that was distributed throughout all of the subjects in the group.

In conclusion, we have shown that isoflurane concentrations of ≥0.6 MAC prevented learning of both factual information and a behavioral suggestion (ear-touching) presented during anesthesia.

We acknowledge the editorial assistance of Winifred von Ehrenburg in preparation of this manuscript.

References

1. Wilson SL, Vaughan RW, Stephen CR. Awareness, dreams and hallucinations associated with general anesthesia. Anesth Analg 1975;54:609–17.
2. Liu WHD, Thorp TAS, Graham SG, Aitkenhead AR. Incidence of awareness with recall during general anaesthesia. Anaesthesia 1991;46:435–7.
3. Anonymous. On being aware (editorial). Br J Anaesth 1979;51:711–2.
4. Bogetz MS, Katz JA. Recall of surgery for major trauma. Anesthesiology 1984;61:6–9.
5. Crawford JS. Awareness during operative obstetrics under general anaesthesia. Br J Anaesth 1971;43:179–82.
6. Crawford JS, Lewis M, Davies P. Maternal and neonatal responses related to the volatile agent used to maintain anaesthesia at caesarean section. Br J Anaesth 1985;57:482–7.
7. Harris TJB, Brice DD, Hetherington RR, Utting JE. Dreaming associated with anaesthesia: the influence of morphine premedication and two volatile adjuvants. Br J Anaesth 1971;43:172–8.
8. Warren TM, Datta S, Ostheimer GW, Naulty JS, Weiss JB, Morrison JA. Comparison of the maternal and neonatal effects of halothane, enflurane and isoflurane for cesarean delivery. Anesth Analg 1983;62:516–20.
9. Newton DEF, Thornton C, Konieczko K, et al. Levels of consciousness in volunteers breathing sub-MAC concentrations of isoflurane. Br J Anaesth 1990;65:609–15.
10. Levinson BW. States of awareness during general anaesthesia. Br J Anaesth 1965;37:544–6.
11. Millar K, Watkinson N. Recognition of words presented during general anaesthesia. Ergonomics 1983;26:585–94.
12. Bennett HL, Davis HS, Giannini JA. Non-verbal response to intraoperative conversation. Br J Anaesth 1985;57:174–9.
13. Goldmann L. Information processing under general anaesthesia: a review. J R Soc Med 1988;81:224–7.
14. Goldmann L, Shah MV, Hebden MW. Memory of cardiac anaesthesia: psychological sequelae in cardiac patients of intraoperative suggestion and operating room conversation. Anaesthesia 1987;42:596–603.
15. Bonke B, Schmitz PIM, Verhage F, Zwaveling A. Clinical study of so-called unconscious perception during general anaesthesia. Br J Anaesth 1986;58:957–64.
16. Evans C, Richardson PH. Improved recovery and reduced postoperative stay after therapeutic suggestions during general anaesthesia. Lancet 1988;2:491–3.
17. McLintock TT, Aitken H, Downie C, Kenny GN. Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. Br Med J (Clin Res) 1990;301:788–90.
18. Block RI, Ghoneim MM, Sum Ping ST, Ali MA. Human learning during general anaesthesia and surgery. Br J Anaesth 1991;66:170–8.
19. Block RI, Ghoneim MM, Sum Ping ST, Ali MA. Efficacy of therapeutic suggestions for improved post-operative recovery presented during general anesthesia. Anesthesiology 1991;75:746–55.
20. Dubovsky SI, Trustman R. Absence of recall after general anesthesia: implications for theory and practice. Anesth Analg 1976;55:696–701.
21. Eich E, Reeves JL, Katz RL. Anesthesia, amnesia and the memory/awareness distinction. Anesth Analg 1985;64:1143–8.
22. Boeke S, Bonke B, Bouwhuis-Hoogerwerf ML, Bovill JG, Zwaveling A. Effects of sounds presented during general anaesthesia on postoperative course. Br J Anesth 1988;60:697–702.
23. Humphreys KJ, Asbury AJ, Millar K. Investigation of awareness by homophone priming during computer controlled anaesthesia. In: Bonke B, Fitch W, Millar K, eds. Memory and awareness in anaesthesia. Amsterdam: Swets, 1990:101–9.
24. Jansen CK, Bonke B, Klein J, et al. Unconscious perception during balanced anesthesia? In: Bonke B, Fitch W, Millar K, eds. Memory and awareness in anaesthesia. Amsterdam: Swets, 1990:115–9.
25. Squire LR. Mechanisms of memory. Science 1986;232:1612–9.
26. Schacter DL. Implicit memory: history and current status. J Exp Psychol (Learn Mem Cogn) 1987;13:501–18.
27. Kihlstrom JF, Schacter DL. Anaesthesia, amnesia, and the cognitive unconscious. In: Bonke B, Fitch W, Millar K, eds. Memory and awareness in anaesthesia. Amsterdam: Swets, 1990:21–44.
28. Frumin MJ. Clinical use of a physiological respirator producing N_2O amnesia-analgesia. Anesthesiology 1957;18:290–9.
29. Mainzer J. Awareness, muscle relaxants, and balanced anaesthesia. Can Anaesth Soc J 1979;26:386–93.
30. Smith RA, Winter PM, Smith M, Eger EI II. Rapidly developing tolerance to acute exposures to anesthetic agents. Anesthesiology 1979;50:496–500.
31. Rupreht J, Dworacek B, Bonke B, Dzoljic MR, Eijndhoven JHM, de Vlieger M. Tolerance to nitrous oxide in volunteers. Acta Anaesthesiol Scand 1985;29:635–8.
32. Avramov MN, Shingu K, Mori K. Progressive changes in electroencephalographic responses to nitrous oxide in humans: a possible acute drug tolerance. Anesth Analg 1990;70:369–74.
33. Theye RA, Michenfelder JD. The effect of nitrous oxide on canine cerebral metabolism. Anesthesiology 1968;29:1119–24.
34. Sakabe T, Tsutsui T, Maekawa T, Ishikawa T, Takeshita H.

Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. Anesthesiology 1985;63:262–6.
35. Pellegrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 1984;60:405–12.
36. Reasoner DK, Warner DS, Todd MM, McAllister A. Effects of nitrous oxide on cerebral metabolic rate in rats anaesthetized with isoflurane. Br J Anaesth 1990;65:210–5.
37. Smith NT, Hoff BH, Rampil IJ, Sasse FJ, Flemming DC. Does thiopental or N_2O disrupt the EEG during enflurane? Anesthesiology 1979;51:S5.
38. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 1975;42:197–200.
39. Kihlstrom JF, Schacter DL, Cork RC, Hurt CA, Behr SE. Implicit and explicit memory following surgical anesthesia. Psychol Sci 1990;1:303–6.

Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® 5 mg/mL Injectable

(diltiazem hydrochloride)

BOLUS INFUSION



GAINS HEART RATE CONTROL QUICKLY...

CIVAH495/A8113

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

Please the see brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAH495/A8113

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action from first bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1†]
- Do not use in Af/Fl patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome and second- or third-degree AV block except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable (diltiazem hydrochloride) BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	**If response is inadequate, wait 15 minutes**	**Treatment as**
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

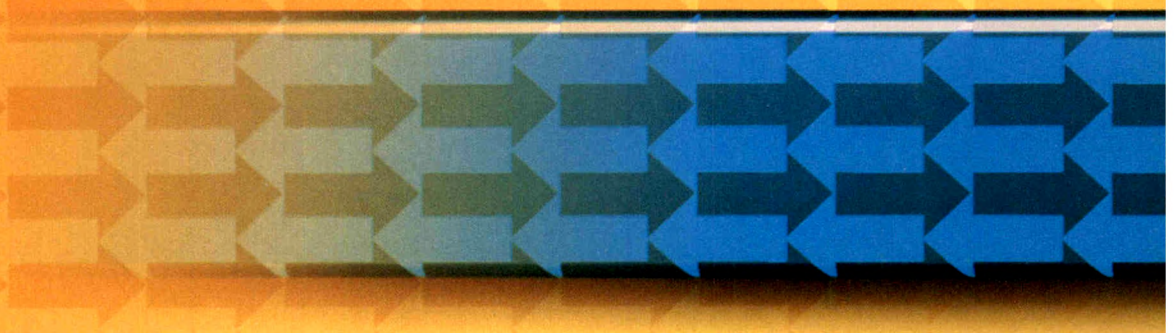
References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

Now in benzodiazepine anesthesia

Take Aim at Prompt Reversal



Introducing from Roche...

Awake and alert–effective reversal of sedation

- New MAZICON (flumazenil/Roche) rapidly and specifically reverses sedation produced by any benzodiazepine
- Promptly restores patients to consciousness—often within minutes of reaching an effective dose
- Reverses benzodiazepine sedative effects only—not the effects of narcotics or other CNS agents

Adverse effects

- The most common side effects in clinical trials were nausea and vomiting (11%), dizziness (10%), agitation (3-9%) and injection-site pain (3-9%)

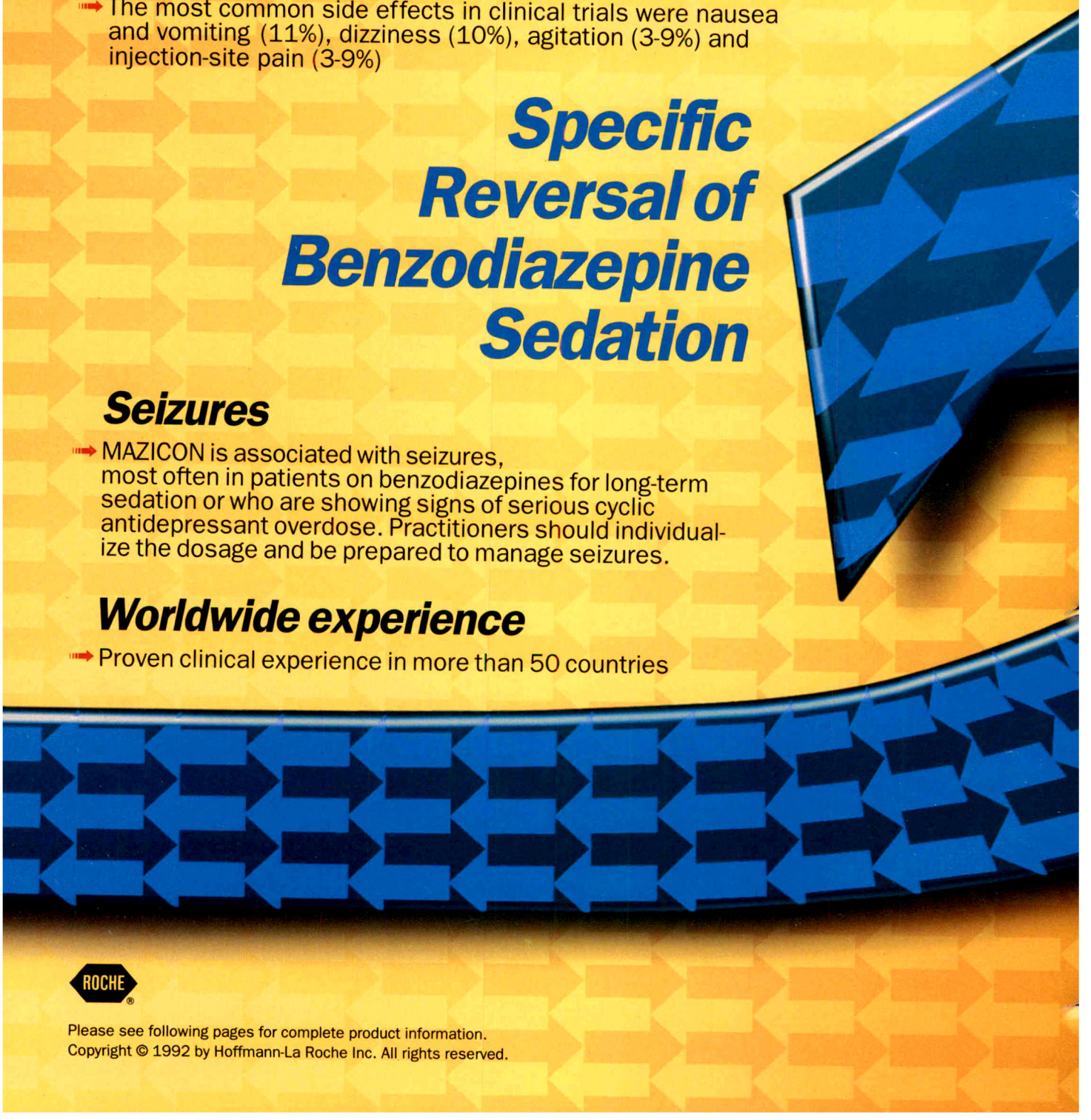
Specific Reversal of Benzodiazepine Sedation

Seizures

- MAZICON is associated with seizures, most often in patients on benzodiazepines for long-term sedation or who are showing signs of serious cyclic antidepressant overdose. Practitioners should individualize the dosage and be prepared to manage seizures.

Worldwide experience

- Proven clinical experience in more than 50 countries



ROCHE®

Please see following pages for complete product information.

Copyright © 1992 by Hoffmann-La Roche Inc. All rights reserved.


1-800-756-7654
Call today for more information.
0.1 mg/mL
Mazicon I.V.
flumazenil/Roche
New
0.1 mg/mL
Mazicon I.V.
flumazenil/Roche
The reversal agent you've been waiting for
See important safety information about resedation.

Prompt Reversal of Benzodiazepine Sedation

Dosing and Administration

For reversal of benzodiazepine-induced general anesthesia or conscious sedation:

Initial dose: 0.2 mg *(2 mL) I.V. over 15 seconds*

➡ *If desired level of consciousness is not obtained after waiting an additional 45 seconds:*

Follow-up doses: 0.2 mg *(2 mL) I.V. every 60 seconds*

➡ *Up to a maximum dose of* ***1.0 mg*** *(10 mL)*

Management of resedation:

Repeat treatment above

Repeat treatment may be given no more often than every 20 minutes

➡ *No more than* ***1 mg*** *total dose should be given in any 5-minute interval*

➡ *No more than* ***3 mg*** *total dose should be given in any one hour*

Important safety information

➡ *Contraindicated in hypersensitivity to benzodiazepines or MAZICON; in patients taking benzodiazepines for control of potentially life-threatening conditions; and in patients showing signs of serious cyclic antidepressant overdose*

➡ *Patients should be monitored for resedation, respiratory depression or other residual effects of benzodiazepines*

➡ *MAZICON does not diminish the need for prompt detection of hypoventilation and the ability to intervene effectively by establishing an airway and assisting ventilation*

➡ *MAZICON should not be the initial treatment for benzodiazepine-induced hypoventilation; the first step is assisted ventilation*

➡ *In patients who are dependent on benzodiazepines, MAZICON may precipitate withdrawal syndromes*

Available in 5-mL and 10-mL vials



New

0.1 mg/mL

Mazicon I.V.™

flumazenil/Roche

The reversal agent you've been waiting for

See important safety information about resedation.

Roche Laboratories

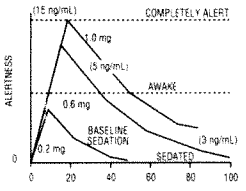
a division of Hoffmann-La Roche Inc.

MAZICON™
(flumazenil/Roche)

DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4] benzodiazepine-3-carboxylate.
Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



Minutes after Flumazenil Injection

*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{ss}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells.
Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng•hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.
The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg.
Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg.

Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness.
MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:
- in patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- in patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES. THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTI-DEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.

Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic anti-depressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely. Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependent on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.) Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance

of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.
USE IN OVERDOSE: MAZICON is intended as an adjunct to, not as a substitute for proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.
Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.
HEAD INJURY: MAZICON should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.
USE WITH NEUROMUSCULAR BLOCKING AGENTS: MAZICON should not be used until the effects of neuromuscular blockade have been fully reversed.
USE IN PSYCHIATRIC PATIENTS: MAZICON has been reported to provoke panic attacks in patients with a history of panic disorder.
PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.
USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (see PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.
USE IN CARDIOVASCULAR DISEASE: MAZICON did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.
USE IN LIVER DISEASE: The clearance of MAZICON is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction (see PHARMACOKINETICS). While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.
USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: MAZICON should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.
MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.
The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.
Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (6 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.
Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndrome for alcohol, barbiturates, and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when MAZICON was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.
Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)
The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.
USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)
Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of MAZICON is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)
INFORMATION FOR PATIENTS: MAZICON does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:
1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.
LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.
DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.
Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.
Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.
PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.
Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weanling was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.
LABOR AND DELIVERY: The use of MAZICON to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

MAZICON™ (flumazenil/Roche)

NURSING MOTHERS: Caution should be exercised when deciding to administer MAZICON to a nursing woman because it is not known whether flumazenil is excreted in human milk.
PEDIATRIC USE: MAZICON is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.
GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of MAZICON in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of MAZICON may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic anti-depressants) as part of an overdose.
Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. MAZICON administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)
Two of the 448 patients who received MAZICON in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).
ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to MAZICON administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).
BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)
CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)
DIGESTIVE SYSTEM: Nausea and Vomiting (11%)
NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).
SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)
All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.
*Indicates reaction in 3% to 9% of cases.
Observed percentage reported if greater than 9%.
The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to MAZICON administration and/or reversal of benzodiazepine effects:
NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).
SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).
The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to MAZICON administration is unknown, but they are included as alerting information for the physician.
BODY AS A WHOLE: Rigors, shivering.
CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.
DIGESTIVE SYSTEM: Hiccup.
NERVOUS SYSTEM: Speech disorder (dysphonia, thick tongue).
Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.
Although MAZICON has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of MAZICON, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.
Reversal with an excessively high dose of MAZICON may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: MAZICON is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If MAZICON is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, MAZICON should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.
REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)
In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.
It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the appropriate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.
Do not rush the administration of MAZICON. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)
Most patients with benzodiazepine overdose will respond to a cumulative dose of 1 to 3 mg of MAZICON, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).
If a patient has not responded five minutes after receiving a cumulative dose of 5 mg MAZICON, the major cause of sedation is likely not to be due to benzodiazepines, and additional MAZICON is likely to have no effect. In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.
SAFETY AND HANDLING: MAZICON is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.
HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

The **American Board of Anesthesiology (ABA)** will administer a written examination in **CRITICAL CARE MEDICINE** on Saturday, September 11, 1993. Diplomates of the ABA who apply and are judged to be qualified by virtue of their additional training will be accepted for examination. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1796. The deadline for receipt of completed applications in the Board office is March 1, 1993.

The **American Board of Anesthesiology (ABA)** will award a Certification of Added Qualifications in **PAIN MANAGEMENT** beginning in 1993. Diplomates of the ABA who apply for the certificate, and are judged to be qualified by virtue of their additional training or experience in Pain Management, will be accepted for the examination to be administered Saturday, September 11, 1993. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1796. The deadline for receipt of completed applications in the Board office is March 1, 1993.

— THE BEN COVINO RESEARCH AWARD —

Applications for up to $10,000 are invited for the 1993 Ben Covino Award, subject to the following basic conditions:

- The proposal should primarily relate to the use of local anesthetics/regional anesthesia, specifically within the preclinical and explorative clinical research fields.
- Applications to the Covino Award Committee must be received in the IARS Cleveland office no later than November 20, 1992. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
2 Summit Park Drive, Suite 140
Cleveland, OH 44131
USA
Telephone: (216) 642-1124

The establishment of the Ben Covino Award was announced at the 1992 Annual Scientific Meeting of the International Anesthesia Research Society held at the San Francisco Hilton. The Ben Covino Award has been instituted by Astra Pain Control, Sweden.

Now available in 20 mg/20 mL vials

THE LOGICAL CHOICE



CRUCIAL PARAMETERS IN SELECTING A NEUROMUSCULAR BLOCKING AGENT

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY		
To 25% of control	25-40 min[3]	35-45 min[5]
To 95% of control	45-65 min[3]	60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

* Dose of atracurium above 0.5 mg/kg is not recommended.
† As originally supplied by the respective manufacturers.
‡ Storage after reconstitution varies with solution. See package insert.

Norcuron®
(vecuronium bromide) for injection

THE LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon ORGANON INC. WEST ORANGE NEW JERSEY 07052

Norcuron®
(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR (MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anaphric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04–0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25–30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succhylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which a so cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{95}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25–30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45–65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04–0.06 mg/kg with inhalation anesthesia and 0.05–0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80–100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20–40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25–60 percent, 45–60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution — Sterile water for injection — Lactated Ringers
5% glucose in water — 5% glucose in saline

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED:

10 mL vials (10 mg vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP).
22 g 1¼" needle. Boxes of 10 NDC No. 0052-0441-60

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).
Boxes of 10 NDC No. 0052-0441-17

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-0441-15
20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-0442-46

STORAGE: 15°–30°C (59°–86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription. REVISED 1/92

References

1. Gallo JA, Cork RC, Puchi P. Comparison of effects of atracurium and vecuronium in cardiac surgical patients. *Anesth Analg.* 1988;67:161–165. 2. Basta SJ, Savarese JJ, Ali HH, et al. Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiol.* 1983;59(3):A273. 3. Norcuron® (vecuronium bromide) for injection package insert. 4. Kaufman JA, Dubois MY, Chen JC, Lea D. Pharmacodynamic effects of vecuronium: A dose response study. *J Clin Anesth.* 1989;1(6):434–439.5. Tracrium* Injection (atracurium besylate) package insert. 6. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anesth.* 1985;57:550–553.

*Tracrium is a registered trademark of Burroughs Wellcome Co.

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

©1992 ORGANON INC.

ORG-13842 PRINTED IN USA FEBRUARY 1992

THE SYNERGY OF CO-INDUCTION

Optimal induction produces 1) unconsciousness and 2) a rapid progression to a state of anesthesia, with maintenance of stable cardiovascular functioning.[1]

However, even though high doses of hypnotics—such as thiopental or propofol—can achieve both endpoints, they can also cause significant hemodynamic changes. Therefore, it may be advantageous to manage hypnosis and anesthesia sequentially by employing a combination of function-specific agents.

Indeed, VERSED given in combination with a second agent can achieve hypnosis through the synergistic interaction of subanesthetic doses,[2-8] the goal being to maximize desired effects and reduce the undesired.

The advantage of co-induction

It is well established that induction agents potentiate each other when given in combination. One quarter of the hypnotic ED_{50} of VERSED can reduce the hypnotic ED_{50} of thiopental by as much as 75%.[3]

However, this degree of reduction occurs when thiopental is given one minute after VERSED, thereby achieving synchronous peak effects. The magnitude of interaction diminishes as the interval between the administration of the co-induction agents lengthens.

Dosing considerations with VERSED® (midazolam HCl/Roche)℞

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

IDEAS IN ANESTHESIA

AN ONGOING SERIES

Please see summary of product information on following page.

References: 1. Wilkinkin RL. Management of general anesthesia. In: Miller RD, ed. *Anesthesia*. 3rd ed. New York: Churchill Livingstone; 1990:1335-1346. 2. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology*. 1990;73(3A):A1216. 3. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1988 67:342-345. 4. Tverskoy M, et al. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth*. 1989; 63:109-112. 5. Short TG, Galletly DC, Plummer JL. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth*. 1991;66:13-19. 6. Kissin I, et al. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg*. 1990;71:65-69. 7. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. 8. Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth*. 1990;64:45-47.

VERSED®
midazolam HCl/Roche ℞
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.
Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.
Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.
WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.
Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.
Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.
Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect.
Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.
Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.
Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.
Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.
VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.
Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.
Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.
PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.
VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.
Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.
Drug Interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.
A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.
IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.
Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.
No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.
Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.
Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.
Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.
Midazolam did not have mutagenic activity in tests that were conducted.
A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.
Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.
Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.
Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.
Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.
Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.
ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.
Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).
IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.
Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.
Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.
OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0891

Roche Laboratories
ROCHE a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Oxygen Consumption and Carbon Dioxide Elimination After Release of Unilateral Lower Limb Pneumatic Tourniquets

Tat-Leang Lee, FFARACS, William A. Tweed, MD, FRCPC, and Bachan Singh, FFARCS
Department of Anaesthesia, National University Hospital, Singapore

Oxygen consumption ($\dot{V}o_2$), carbon dioxide elimination ($\dot{V}co_2$), and respiratory exchange ratio (RQ) were continuously measured in 15 male and 15 female adults during knee surgery, with the leg exsanguinated by an inflatable tourniquet around the thigh. Arterial blood was also intermittently sampled for blood gas analysis, electrolytes, and lactate content before and after tourniquet deflation. There was a significant increase in $\dot{V}o_2$ and $\dot{V}co_2$ after tourniquet deflation, which was more pronounced in the male (aged 29.5 ± 14.8 yr, mean ± SD) than the female (aged 56.9 ± 15.6 yr) patients, both in terms of maximal increase ($P < 0.001$) and percent of increase from values before deflation ($P < 0.001$ and $P = 0.01$). The body weights and tourniquet inflation times were not significantly different between the male and female patients. Excess $\dot{V}o_2$ (O_2 debt) and excess $\dot{V}co_2$ over 12 min after deflation of the tourniquet were also significantly higher for male (593.5 ± 222.9 mL and 714.9 ± 463.8 mL, respectively) than for female patients (302 ± 73.3 mL and 196 ± 162.22 mL, respectively; $P < 0.01$). There was no correlation between the duration of tourniquet inflation time and peak increase in $\dot{V}o_2$, peak increase in $\dot{V}co_2$, and O_2 debt over 12 min after deflation of the tourniquet; however, tourniquet time was weakly correlated with excess $\dot{V}co_2$ over 12 min after tourniquet deflation ($r = 0.55$, $P = 0.002$). There was a significant decrease in pHa ($P < 0.001$) from release of $Paco_2$ and lactate after tourniquet deflation. Plasma potassium levels also increased significantly after tourniquet release ($P < 0.01$). All of these biochemical changes did not cause any adverse effects in the study patients. In view of the predictable increase in $\dot{V}o_2$ and $\dot{V}co_2$, we recommend monitoring of end-tidal CO_2 and a transient increase in minute ventilation to maintain normocapnea.

(Anesth Analg 1992;75:113–7)

Orthopedic surgery of the lower extremities frequently requires exsanguination and the use of pneumatic tourniquets. Several studies reported significant but transient increases in $Paco_2$ (1–3) and end-tidal CO_2 ($ETco_2$) (4–6) in children and adults after tourniquet deflation. This is assumed to represent washout of accumulated metabolic waste products from the ischemic limb. There is little information published with regard to the actual amount of CO_2 produced and change in oxygen (O_2) consumption after such an ischemic event. The object of this clinical study was to investigate the change in lower limb skeletal muscle metabolism (O_2 consumption [$\dot{V}o_2$] and CO_2 elimination [$\dot{V}co_2$]) after tourniquet deflation in unilateral lower extremity surgery.

Accepted for publication March 4, 1992.

Address correspondence to Dr. Lee, Department of Anaesthesia, National University Hospital, 5 Lower Kent Ridge Road, Singapore 0511.

Methods

After obtaining institutional ethics committee and written, informed patient consent, 15 male and 15 female adults (ASA physical status I–II) scheduled for surgical procedures on the lower extremities that involved the use of pneumatic tourniquets were selected. Male patients had arthroscopic surgery for knee problems related to sport injuries, whereas female patients had arthroscopic debridement due to degenerative diseases of the knee joints. The extremity undergoing surgery was exsanguinated with an Esmarch bandage and the pneumatic tourniquet inflated to a pressure of 450 mm Hg. Patients with known cardiac, pulmonary, or renal disease were excluded from this study.

Anesthesia was induced with propofol (1.5–2.5 mg/kg IV), and tracheal intubation was facilitated by intravenous administration of alcuronium. Anesthesia was maintained with propofol infusion (6–10 mg/kg), and analgesia was provided by fentanyl or morphine. The lungs were ventilated with 40% O_2

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

in air with a Siemens Servo 900 C ventilator to maintain an $ETco_2$ at approximately 30 mm Hg with a Siemens CO_2 analyzer model 930. Patient monitoring systems included an electrocardiogram, a nasopharyngeal temperature probe, a blood pressure sphygnomanometer (DINAMAP), and pulse oximetry. Oxygen consumption ($\dot{V}o_2$), CO_2 elimination ($\dot{V}co_2$), and respiratory exchange ratio (RQ = $\dot{V}co_2/\dot{V}o_2$) were continuously monitored with a gas exchange monitor (Deltatrac, Datex/Instrumentatrium, Helsinki, Finland) after induction of anesthesia and tourniquet inflation and for 12 min after deflation. Nitrous oxide and inhaled agents were excluded because they can affect the performance of the gas exchange monitor. The Deltatrac is an open-system indirect calorimetry device designed for measurements of $\dot{V}o_2$ and $\dot{V}co_2$ in both spontaneously breathing and mechanically ventilated patients. The values for $\dot{V}o_2$ and $\dot{V}co_2$ are updated by the Deltatrac every minute; $\dot{V}o_2$ and $\dot{V}co_2$ are expressed under standard conditions: dry gas at 0°C and 760 mm Hg (STPD). Excess $\dot{V}o_2$ and $\dot{V}co_2$ were calculated as the total amount of $\dot{V}o_2$ and $\dot{V}co_2$ over 12 min after tourniquet deflation in excess of their respective immediate values before deflation.

After induction of anesthesia, a 20-gauge catheter was placed in a radial artery for blood sampling. Blood samples were sent immediately after withdrawal for measurements of pH, Pao_2, $Paco_2$, sodium (Na^+), potassium (K^+), and ionized calcium (Ca^{2+}) by a Nova Biomedical Stat Profile blood gas and electrolytes analyzer at 37°C just before and 5 and 10 min after deflation of the pneumatic tourniquet. Blood samples were also sent for measurements of lactate (enzymatic assay) levels immediately preceding and 5 and 10 min after deflation. All measuring instruments were appropriately calibrated.

Demographic data, duration of tourniquet inflation, and variables of $\dot{V}o_2$ and $\dot{V}co_2$ for male and female patients were compared by unpaired *t*-tests. Changes in arterial blood gas values, electrolytes, lactate content, $\dot{V}o_2$, $\dot{V}co_2$, and RQ before and after tourniquet deflation were compared by analysis of variance and least significant differences test. Linear regression analysis was used to correlate tourniquet time and variables for $\dot{V}o_2$ and $\dot{V}co_2$. A *P* value <0.05 was considered to be statistically significant. All values are reported as mean ± SD unless otherwise stated.

Results

Male patients were significantly younger than female patients (Table 1). Body weights and tourniquet inflation times were not significantly different between the two groups (Table 1). The $\dot{V}o_2$ and $\dot{V}co_2$ values increased significantly in all patients after deflation of the pneumatic tourniquets (Figure 1) and had not returned to baseline values before deflation by 12 min after deflation, when the measurements were stopped. The RQ values decreased for 4 min after tourniquet deflation (Figure 2).

Table 1. Clinical Data and Duration of Tourniquet Inflation in 30 Patients Undergoing Lower Extremity Surgery

	Male (n = 15)	Female (n = 15)
Age (yr)	29.5 ± 14.8	56.9 ± 15.6[a]
Weight (kg)	63.1 ± 8.9	61.2 ± 9.8
TT (min)	102.5 ± 46 (22–180)	92.6 ± 28 (21–122)

TT, tourniquet time.
Data are expressed as mean values ± SD. Values in parentheses indicate range.
[a] $P < 0.0001$.

Values before deflation, peak values after deflation, and percent increase in $\dot{V}o_2$ and $\dot{V}co_2$ were significantly higher in male patients (Table 2). The excess O_2 consumption (O_2 debt) and excess CO_2 elimination over 12 min after tourniquet deflation were also significantly higher for male patients (593.5 ± 222.9 mL and 714.9 ± 463.8 mL, respectively) than for female patients (302 ± 173.3 mL and 196 ± 102.22 mL, respectively; $P < 0.001$) (Figure 3). There was no correlation between the duration of tourniquet time and the peak increase in $\dot{V}o_2$, peak increase in $\dot{V}co_2$, and O_2 debt over 12 min after deflation of the tourniquet; however, tourniquet time was weakly correlated with excess CO_2 elimination over 12 min after tourniquet deflation ($r = 0.55$, $P = 0.002$).

The pHa ($P < 0.001$) and standard blood bicarbonate ($P < 0.01$) decreased, and $Paco_2$ ($P < 0.001$), serum potassium ($P < 0.01$), and lactate ($P < 0.001$) increased; Pao_2 and O_2 saturation did not show significant changes (Table 3). There was a transient but insignificant decrease in arterial blood pressure and increase in heart rate after tourniquet deflation.

Discussion

The gas exchange monitor (Deltatrac) used in this study has recently been validated (7). This monitor allows continuous monitoring of $\dot{V}o_2$ and $\dot{V}co_2$. Nitrous oxide and inhaled anesthetics that could affect CO_2 and O_2 analysis were excluded from the anesthetic technique. Our results showed a significant

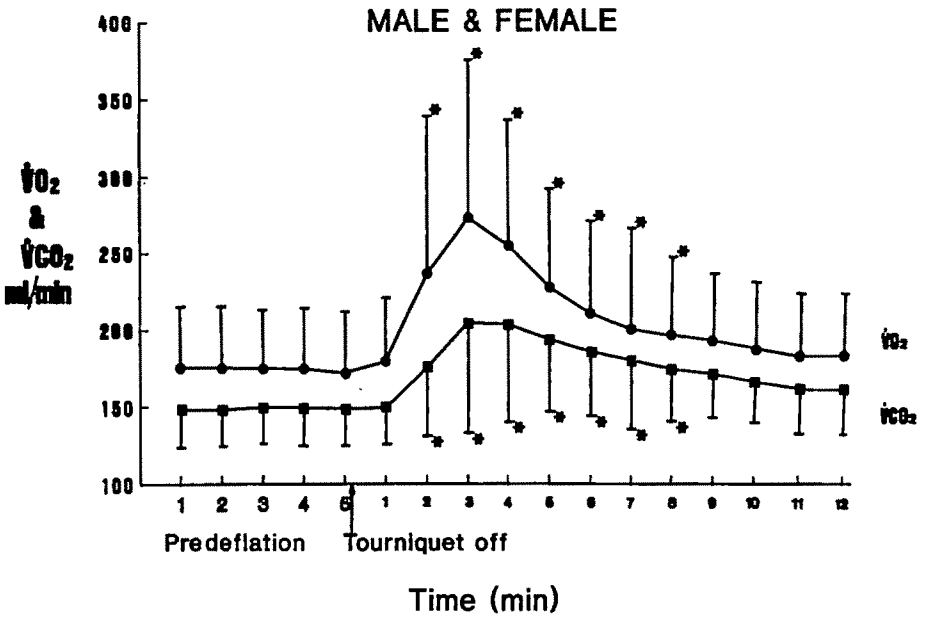


Figure 1. Changes in O_2 consumption ($\dot{V}o_2$) and CO_2 elimination ($\dot{V}co_2$) after tourniquet deflation. *Asterisks* indicate values that are significantly different ($P < 0.05$) from those immediately before tourniquet deflation.

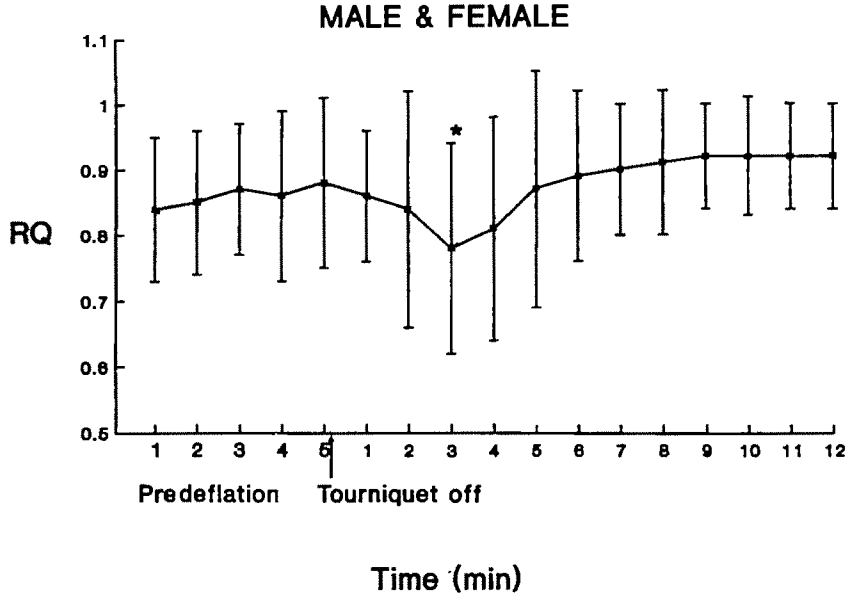


Figure 2. Changes in respiratory exchange ratio (RQ) after tourniquet deflation. *Asterisk* indicates value significantly different ($P < 0.05$) from those immediately before tourniquet deflation.

increase in $\dot{V}o_2$ and $\dot{V}co_2$ after tourniquet deflation that was more pronounced in the younger male than the older female patients, both in terms of maximal increase and percentage of increase from values before deflation. This was presumably due to the larger muscle mass in the male patients who were younger and had arthroscopic surgery after sport injuries. The female patients had knee surgery related to chronic degenerative knee diseases that were invariably associated with atrophy from disuse of the muscles of the lower limbs.

After tourniquet release, Pao_2 was reported to decrease significantly in elderly patients who were breathing spontaneously with Fio_2 of 0.28 (1) or to remain unchanged in children who were mechanically ventilated (3). There was no significant change in Pao_2 in our patients ($Fio_2 = 0.5$), but we observed a significant increase in $\dot{V}o_2$. The increase in $\dot{V}o_2$ was

Table 2. Comparison of Variables of O_2 Consumption ($\dot{V}o_2$) and CO_2 Elimination ($\dot{V}co_2$) Between 15 Male and 15 Female Patients

	$\dot{V}o_2$ (mL/min)			$\dot{V}co_2$ (mL/min)		
	Male	Female	*P* value	Male	Female	*P* value
Before deflation (A)	195.4 ± 26.1	145.9 ± 32.6	<0.001	158.4 ± 18.5	129.8 ± 20.2	<0.001
Peak value after deflation (B)	372.4 ± 73.9	215.7 ± 56.6	<0.001	256.4 ± 66.2	168.3 ± 35.1	<0.001
% Increase = [(B − A)/A] × 100	89.6 ± 21.3	48.7 ± 28.9	<0.001	46.5 ± 41	29.2 ± 12.8	0.01

Data are presented as mean values ± SD.

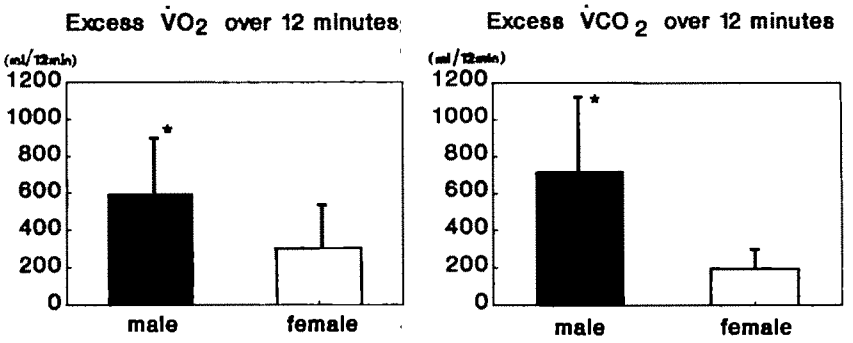


Figure 3. Comparison of excess O_2 consumption ($\dot{V}o_2$) and CO_2 elimination ($\dot{V}co_2$) over 12 min after tourniquet deflation between male and female patients. *$P < 0.001$.

Table 3. Changes in Arterial Blood Gas Values, Electrolytes, and Lactate Content After Tourniquet Deflation

	Before deflation	Minutes after deflation	
		5	10
pH	7.43 ± 0.05	7.35 ± 0.05[a]	7.39 ± 0.05[a]
$Paco_2$ (mm Hg)	34.5 ± 5.5	41.7 ± 6.7[a]	37.7 ± 5.0[a]
Pao_2 (mm Hg)	167.5 ± 37.4	172.2 ± 35.9	164.6 ± 38.4
SBC (mM/L)	24.3 ± 1.67	22.9 ± 1.2[b]	23.5 ± 1.6[b]
O_2 saturation (%)	99.3 ± 0.68	99.2 ± 0.84	99.2 ± 0.9
Sodium (mmol/L)	142.9 ± 2.3	143.9 ± 2.9	143.6 ± 2.1
Potassium (mmol/L)	3.52 ± 0.3	3.77 ± 0.32[b]	3.65 ± 0.26[b]
Calcium (mmol/L)	1.13 ± 0.13	1.17 ± 0.15	1.16 ± 0.12
Lactate (mmol/L)	2.1 ± 0.66	3.4 ± 0.96[a]	3.10 ± 0.76[b]

SBC, standard blood bicarbonate.
Data are expressed as mean values ± SD.
[a] $P < 0.001$, compared with values before deflation.
[b] $P < 0.01$, compared with values before deflation.

presumably used to replenish the high-energy phosphate pool, which was depleted during the period of ischemia to the lower extremity. The anaerobic metabolism of the ischemic limb caused an O_2 debt. When aerobic condition was reinstituted, the O_2 debt was reflected as increased $\dot{V}o_2$. The O_2 debt was also reflected in the respiratory exchange ratio. When aerobic condition is reinstituted, the RQ will be low until the O_2 debt has been paid. We did not observe a positive correlation between the duration of tourniquet time and peak increase in $\dot{V}o_2$ or O_2 debt over 12 min after tourniquet deflation. This is perhaps due to the continuous decrease in temperature in the nonperfused extremity, which causes a decrease in the metabolic rate of the ischemic skeletal muscle and partly protects the tissues against the harmful effects of anoxia (8). Haljamäe and Enger (9) performed needle biopsies of human skeletal muscle during and after tourniquet ischemia of the lower extremities. They observed a decreased rate of metabolite accumulation and high-energy phosphate reduction with increasing tourniquet time.

Several recent studies reported a significant increase in $ETco_2$ after tourniquet deflation (4–6), which was assumed to reflect an increase in $\dot{V}co_2$. Using the Deltatrac, we were able to monitor the $\dot{V}co_2$ every minute and observed a significant increase in $\dot{V}co_2$ after tourniquet deflation. Dickson et al. (6) found no correlation between the duration of tourniquet time and increase in $ETco_2$; however, Bourke et al. (5) found that tourniquet time was correlated with estimated excess CO_2 elimination and maximal increase in $ETco_2$. Our results showed that although there was a weak correlation between tourniquet time and excess CO_2 elimination, there was no correlation

between tourniquet time and peak increase in $\dot{V}co_2$. The increase in $\dot{V}co_2$ was probably due to the release of accumulated acid metabolites on reperfusion of the extremity (9) and to a hypermetabolic state on recirculation (6).

Our arterial blood gas results show, as do those of others, a significant decrease in pHa contributed by a significant increase in $Paco_2$ and lactate (1–3). Among the serum electrolytes studied, only potassium levels increased significantly after tourniquet release; however, the increase was mild and was within the clinically acceptable limits.

In conclusion, our study demonstrates that there is a significant but transient increase in $\dot{V}o_2$ and $\dot{V}co_2$ after the release of a lower extremity tourniquet. This increase is significantly higher in younger male patients compared with older female patients. A sudden increase in $\dot{V}co_2$ may have detrimental effects in certain patients, such as patients with head injuries with an elevated intracranial pressure. These patients frequently undergo orthopedic and other procedures on the extremities with an pneumatic tourniquet in place (6). We recommend monitoring of $ETco_2$ and transient increase in minute ventilation to maintain normocapnea.

References

1. Modig J, Kolstad K, Wigren A. Systemic reactions to tourniquets ischaemia. Acta Anaesthesiol Scand 1978;22:609–14.
2. Lynn AM, Fischer T, Brandford HG, Pendergrass TW. Systemic responses to tourniquet release in children. Anesth Analg 1986;65:865–72.
3. Brustowicz RM, Moncorge C, Koka BV. Metabolic responses to tourniquet releases in children. Anesthesiology 1987;67:792–4.
4. Patel A, Choi C, Giuffrida JG. Changes in end-tidal CO_2 and arterial blood gas levels after release of tourniquet. South Med J 1987;80:213–6.
5. Bourke DL, Silberberg MS, Ortega R. Respiratory responses associated with release of intraoperative tourniquets. Anesth Analg 1989;69:541–4.
6. Dickson M, White M, Kinney W, Kambam JR. Extremity tourniquet deflation increases end-tidal Pco_2. Anesth Analg 1990; 70:457–8.
7. Takala J, Keinanen O, Vaisanen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. Crit Care Med 1989;17:1041–7.
8. Bruner JM. Time, pressure and temperature factors in the safe use of the tourniquet. Hand 1970;3:39–45.
9. Haljamäe H, Enger E. Human skeletal muscle energy metabolism during and after complete tourniquet ischemia. Ann Surg 1975;182:9–14.

Risk of Human Immunodeficiency Virus in Surgeons, Anesthesiologists, and Medical Students

John M. Buergler, BA, Robert Kim, AB, Ronald A. Thisted, PhD, Stephan J. Cohn, MD, J. Lance Lichtor, MD, and Michael F. Roizen, MD

Department of Anesthesia and Critical Care and Department of Statistics, University of Chicago, Chicago, Illinois

We postulated that three factors determine the occupational risk of infection from the human immunodeficiency virus (HIV) for surgeons, anesthesiologists, and medical students: first, the risk of needlestick exposure per year (range for surgeons 3.8–6.2, weighted average 4.2; range for anesthesiologists 0.86–2.5, weighted average 1.3; range for third-year medical students 0–5, best estimate 5); second, the risk of seroconversion from a needlestick exposure (0.42%–0.50%); and third, prevalence of HIV in the population served (0.32%–23.6%, depending on geographic location). Thus, the calculated range for occupational risk of HIV infection for a surgeon over a 30-yr period (assuming no change in HIV prevalence or benefit from protective measures) was 0.17%–13.9%; for an anesthesiologist, 0.05%–4.50%. The corresponding range of occupational risk for a medical student during the third year was 0.007%–0.59%. The range of risk is large because the variation in prevalence of HIV infection from one area to another is great. The authors validated the methodology first by using an equation, with estimates from the literature for factors in the equation, to calculate the risk of infection for hepatitis B and then by comparing the results with known rates of infection in the prevaccine era. Calculated occupational risk of hepatitis B infection for anesthesiologists was in the lower range of actual prevalence of infection (calculated range 2.32%–20.6%; known range 6%–26%). Calculated risk versus prevalence for surgeons was fairly close (7.31%–53.4% versus 24.4%). The prevalence of HIV infection, however, is estimated to be increasing between 4% and 8.6% annually, causing the 30-yr risk for surgeons to increase to 0.32%–0.71% in low-prevalence work sites and to 24.4%–36.4% in high-prevalence work sites. For anesthesiologists, the 30-yr risks increase to 0.10%–0.22% in low-prevalence areas and to 8.26%–13.0% in high-prevalence areas; for third-year medical students, the 1-yr estimates are 0.001%–0.007% for low-risk areas and 0.12%–0.59% for high-risk areas. Double gloving reduces the risks of a needlestick exposure in surgeons by 57%–92% (average 80%). Thus, over 30 yr, the calculated occupational risks for a surgeon decrease (even assuming a 4% annual increase in prevalence of HIV infection) from 0.32% to 0.06% in low-risk areas and from 24.4% to 5.41% in high-risk areas; the risks for an anesthesiologist might similarly be postulated to decrease from 0.10% to 0.02% in low-risk areas and from 8.26% to 1.71% in high-risk areas. For a third-year medical student in a low-risk area, the decrease is from 0.0013% to 0.0003%, and for one in a high-risk area, the decrease is from 0.59% to 0.12%. Even with double gloving, these risks are substantially greater than those for other public safety officers (i.e., policemen and firemen). Geographic location, type of needlestick exposure (glancing versus puncture), and adherence to safety procedures such as double gloving may be important determinants of actual risk. Based on the published data for hepatitis B infection, the calculated risk for HIV infection may be correct for surgeons, underestimated for anesthesiologists, and still unresolved for third-year medical students. More secure estimates could be afforded if more data were available for number of needlesticks per year and for the reduction of risk by use of safety precautions. If the occupational risk of HIV infection for anesthesiologists is as great as that for surgeons, double-gloving precautions may have as great a benefit.

(Anesth Analg 1992;75:118–24)

The increasing prevalence of acquired immunodeficiency syndrome (AIDS) has heightened concern over the risk of transmitting human immunodeficiency virus (HIV) between patient and health care professional. We estimated the range of occupational risk of HIV infection for surgeons, anesthesiologists, and third-year medical students by reviewing the literature for prevalence of disease, number of hours worked, rates of exposure per hour or year worked, rates of infection per exposure, and efficacy of various preventive measures. Using these values, we then devised equations to estimate the range of occupational risk of HIV infection for 1 and 30 yr.

Accepted for publication March 4, 1992.

Address correspondence to Dr. Roizen, Department of Anesthesia and Critical Care, University of Chicago, 5841 South Maryland Avenue, Box 428, Chicago, IL 60637.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Frequent exposure to blood and body fluids and frequent use of needles may increase the risk of HIV infection for anesthesiologists. Likewise, risk may also be high for third-year medical students, who routinely draw blood and assist during surgery and obstetric deliveries. Moreover, lack of familiarity with procedures further increases a student's risk of percutaneous needle exposure (1,2). We also investigated the hypothesis that surgeons represent a higher risk group than other physicians. To test the accuracy of our equations, we calculated the theoretical risk of hepatitis B infection for surgeons and anesthesiologists and compared our estimates with known rates of prevalence for hepatitis B in the prevaccine era. As the prevalence of HIV infection is increasing in the United States from 4% to 8.6% annually, we estimated the occupational risk using three different rates of change in prevalence: 0%, 4%, and 8.6%.

Finally, we evaluated the benefit of current preventive measures for reducing the risk of infection. In doing so, we discuss the degree of confidence health care professionals may have in measures such as avoiding contact with blood and body fluids and double gloving for protection against occupational risk of infection.

Methods

To calculate the risk of HIV infection for surgeons, anesthesiologists, and medical students, we derived the following formula for the probability of becoming HIV seropositive in a single year while serving a single surgical population:

$$p_t = r_{exp} \times h_t \times e \times s.$$

In this formula, p_t denotes the probability of developing serologic indicators of HIV ("seroconversion") during year t; r_{exp} denotes the risk of seroconversion per parenteral exposure (needlestick injury) to HIV-infected blood or body fluids; h_t denotes the prevalence of HIV-positive patients during year t in the surgical population of interest; and e represents the number of exposures per year. For surgeons, e is based on 1000 operating-room hours per year. Finally, s is a factor between 0 and 1 that represents the effect of taking safety precautions. To assess the effect of precautions that reduce exposure rates by 80% for instance, we set $s = 0.20$.

In general, the n-year risk for seroconversion is given by

$$p(n) = 1 - [(1 - p_1)(1 - p_2) \cdots (1 - p_n)].$$

If HIV prevalence remains unchanged over a period of n years, then p_t does not change, and the formula simplifies. In this case, the n-year risk can be calculated as

$$p_c(n) = 1 - (1 - p_1)^n,$$

where p_1 is the risk in year 1 calculated from the first formula in this section. Thus, assuming no increase in HIV prevalence, the probability of seroconverting in 30 yr is given by $p_c(30) = 1 - (1 - p_1)^{30}$.

If HIV prevalence grows at a fixed rate per year, then

$$h_t = (1 + y)h_{t-1} = (1 + y)^{t-1} \times h_1,$$

where y is the annual rate of growth, limited so that h_t never exceeds 1. In this case, the general formula for n-year risk must be used, as p_t changes each year. We denote the n-year risk under this assumption by $p_g(n)$. By varying the assumed prevalences, rates of growth, and effect of taking precautions, we can assess the range of plausible risks to which physicians in different specialties, practices, and locations might reasonably expect to be exposed.

We then reviewed the literature to obtain the necessary data, searching the following data bases: Medline (Knowledge Finder software for 1986–1991), for articles on risk of infection for surgeons, anesthesiologists, and medical students; Science Citation Index (Institute for Scientific Information, Philadelphia, Pa.) for 1978–1990; and Medline (National Library of Medicine, Bethesda, Md.) for 1984–1990. The second Medline search used the key words and phrases anesthetist, anesthesiologist, medical student, seroconversion, and human immunodeficiency virus. Because of discrepancies in data from these different sources, we calculated ranges for the risk of HIV infection.

To estimate exposure rate, we used a weighted average, derived from individual studies in which reported frequency of needlestick exposures varied. For example, if 42 anesthesiologists had a mean exposure rate of 0.86 and 16 anesthesiology residents had a mean exposure rate of 2.5, the weighted average exposure rate was 1.3.

To determine the accuracy of our formula and to verify our data, we used the same equation to calculate the theoretical risk of infection for another virus, hepatitis B. We compared these estimates with actual rates of prevalence reported in the literature.

Results

Risk of HIV Infection

According to a combination of studies, the risk of HIV infection after mucous membrane exposure or parenteral inoculation of HIV-infected blood or body fluids is approximately one seroconversion per 200 inci-

Table 1. Risk of HIV Infection for Surgeons Over a 1- and 30-Year Period, Assuming 1000 Operating Room Hours, 4.2 Needlesticks[a] Each Year, and 0%–8.6% Annual Growth in HIV Prevalence

Seroconversion per parenteral exposure to infected blood[b] (%)	HIV-infected patients in population[c] (%)	With single gloves				With double gloves			
			30-yr risk by growth rates				30-yr risk by growth rates		
		1-yr risk (%)	0%/yr (%)	4%/yr (%)	8.6%/yr (%)	1-yr risk (%)	0%/yr (%)	4%/yr (%)	8.6%/yr (%)
0.42	0.32	0.006	0.17	0.32	0.71	0.001	0.03	0.06	0.14
	3.0	0.053	1.58	2.93	6.49	0.011	0.32	0.59	1.33
	5.0	0.088	2.61	4.83	10.6	0.018	0.53	0.98	2.21
	23.6	0.416	11.8	20.9	31.6	0.083	2.47	4.57	7.27
0.50	0.32	0.007	0.20	0.38	0.85	0.001	0.04	0.08	0.17
	3.0	0.063	1.87	3.47	7.68	0.013	0.38	0.70	1.58
	5.0	0.105	3.10	5.72	12.5	0.021	0.63	1.17	2.62
	23.6	0.496	13.9	24.4	36.4	0.099	2.93	5.41	8.60

[a]Range 3.8–6.2; see text and References 2, 4, and 10.
[b]Range in the literature; see text and References 3–5.
[c]Range 0.32%–23.6%; see text and References 6–8.

dents (0.5%) (3). Two other sources made similar estimates: one of 0.42% (4), another of 0.40% (5).

With regard to the prevalence of HIV infection in the general surgical population, analysis of admissions from the emergency room of one metropolitan East Coast hospital showed a rate of 5% (6); however, other studies estimate prevalence to be <3%, depending on geographic location (7). For example, reported rates of HIV infection were as low as 0.32% for hospitals in the Midwest (8) and as high as 23.6% for hospitals in San Francisco (7). The rate of HIV prevalence in the population to which physicians are exposed may increase or remain stable, with the range of increase in the United States estimated at 4%–8.6% annually (9).*

On average, surgeons have 4.2 parenteral injuries per 1000 operating room (OR) hours, the approximate number of hours a surgeon spends in the OR in 1 yr (2,4,10). Substituting these figures into our formula and assuming no increase to an 8.6% increase in prevalence, we found the 30-yr risk of HIV infection for surgeons who do not double glove to range between 0.17% and 0.7% for low-prevalence work sites and between 13.9% and 36.4% for high-prevalence work sites (Table 1).

For anesthesiologists averaging 1.3 parenteral injuries a year (2,11) and assuming a 0% to 8.6% increase in prevalence, the ranges for 30-yr risk of HIV infection without double gloving were 0.05%–0.22% in low-prevalence work sites and 4.5%–13.0% in high-prevalence work sites (Table 2). This value is approximately three times less than that for surgeons and is directly related to estimated difference in needlestick exposures.

Medical students sustain zero to five percutaneous needlesticks in the third year of medical school, a time at which they are first required to perform tasks exposing them to infectious blood (12). Without the use of gloves, and assuming five percutaneous needlesticks per year, we estimated the risk of HIV infection to be 0.007%–0.59%; assuming one percutaneous needlestick injury per year, the risk would be 0.001%–0.12% (Table 3).

Testing the Formula and Estimates for Factors in the Formula Using Data on Hepatitis B

The prevalence of hepatitis B infection, as indicated by positive serologic markers of the virus, is estimated to be 3%–5% of the general population (13,14). Using the average of 1.3 parenteral injuries a year for anesthesiologists, we calculated their incremental risk of hepatitis B infection to be 2.28%–20.6% over a 10-yr period (Table 4). The actual reported prevalence of hepatitis B infection among anesthesiologists is 10%–30% (15),† or an incremental prevalence due to occupational risk of 6%–26%. Our calculations are at the lower range of actual occupational risk of hepatitis B for anesthesiologists.

We calculated the 10-yr occupational risk of hepa-

*The Centers for Disease Control estimated the prevalence of HIV infection in the U.S. population to be approximately 750,000 in January 1986 and 1,000,000 in July 1989, an annualized increase of 8.6%. This rate may decrease in the future as awareness of preventive measures increases and precautions are taken or as early treatment with AZT or alternatives decreases seroconversion; the rate may increase as treatment prolongs the life span of HIV-infected patients.

†The reported prevalence did not include the length of time the anesthesiologists or surgeons surveyed were in practice, but the mean could be estimated to be approximately 10 yr in the prevaccine era (16,17).

Table 2. Risk of HIV Infection for Anesthesiologists Over a 1- and 30-Year Period, Assuming 1.3 Needlesticks[a] Each Year and 0%–8.6% Annual Growth in HIV Prevalence

Seroconversion per parenteral exposure to infected blood[b] (%)	HIV-infected patients in population[c] (%)	Without gloves				With double gloves			
			30-yr risk by growth rates				30-yr risk by growth rates		
		1-yr risk (%)	0%/yr (%)	4%/yr (%)	8.6%/yr (%)	1-yr risk (%)	0%/yr (%)	4%/yr (%)	8.6%/yr (%)
0.42	0.32	0.002	0.05	0.10	0.22	<0.001	0.01	0.02	0.04
	3.0	0.016	0.49	0.91	2.05	0.003	0.10	0.18	0.41
	5.0	0.027	0.82	1.52	3.40	0.005	0.16	0.31	0.69
	23.6	0.129	3.79	6.98	11.0	0.026	0.77	1.44	2.31
0.50	0.32	0.002	0.06	0.12	0.26	<0.001	0.01	0.02	0.05
	3.0	0.020	0.58	1.09	2.44	0.004	0.12	0.22	0.49
	5.0	0.033	0.97	1.81	4.03	0.007	0.19	0.36	0.82
	23.6	0.153	4.50	8.26	13.0	0.031	0.92	1.71	2.74

[a]Range 0.86–2.5; see text and References 2 and 11.
[b]Range in the literature; see text and References 3–5.
[c]Range 0.32%–23.6%; see text and References 6–8.

Table 3. Risk of HIV Infection for Medical Students During the Third Year of Medical School, Assuming 1 or 5 Needlesticks[a] Each Year

Seroconversion per parenteral exposure to infected blood[b] (%)	HIV-infected patients in population[c] (%)	Without gloves		With double gloves	
		1 Needlestick (%)	5 Needlesticks (%)	1 Needlestick (%)	5 Needlesticks (%)
0.42	0.32	0.0013	0.0067	0.0003	0.0013
	3.0	0.013	0.0630	0.0025	0.013
	5.0	0.021	0.11	0.0042	0.021
	23.6	0.099	0.50	0.0198	0.099
0.50	0.32	0.0016	0.0080	0.0003	0.0016
	3.0	0.0150	0.075	0.003	0.0150
	5.0	0.0250	0.13	0.005	0.0250
	23.6	0.12	0.59	0.0236	0.12

[a]Range 0–5; see text and References 2 and 12.
[b]Range in the literature; see text and References 3–5.
[c]Range 0.32%–23.6%; see text and References 6–8.

titis B for surgeons who averaged 4.2 parenteral injuries a year to be 7.35%–53.4% (Table 5). These figures span the actual reported prevalence of 28.4% among surgeons attending American Medical Association conventions at three locales (16),† or a prevalence greater than that in the general population of 24.4%.

The risk of hepatitis B for third-year medical students ranged from 0.18% to 8.75% (Table 6). These figures correspond to the reported prevalence of hepatitis B in noninoculated physicians at the start of surgery or anesthesiology residencies (13,14,16–18) and are compatible with values reported near or at the start of anesthesiology residency (9.4%), after exposure to both the third- and fourth-year medical curricula (18).

Use of universal precautions should—and double gloving does—reduce the risk of percutaneous needlestick exposure in surgeons by 57%–92% (average 80%) (19,20). For every 1% increase in the use of universal precautions on a medical inpatient floor, the risk of actual exposure decreased by approximately 1% (21). Although most exposures on a medical inpatient floor are not related to needlesticks, needlestick exposures decreased at a similar rate; these data are the best we have on the effectiveness of universal precautions in reducing the risk of exposure for surgeons and anesthesiologists. Although following universal precautions is far from universal now (22), education increases the use of precautions to >80% (22,23). With an 80% reduction in risk with the universal use of precautions, and assuming the 4% median rate of annual increase in the prevalence of HIV infection, the range of risk of infection over 30 yr for surgeons is 0.06%–5.41% and for anesthesiologists, 0.02%–1.71%. For the medical student, the risk is 0.0003%–0.12% for the third year (Tables 1–3).

Table 4. Risk of Hepatitis B Infection for Nonimmunized Anesthesiologists Over a 10-Year Period, Assuming No Increase in Prevalence and an Average of 1.3 Needlesticks[a] Each Year

Seroconversion per parenteral exposure to infected blood[b] (%)	Infected patients in population[b] (%)	1-yr risk of infection (%)	10-yr risk of infection[c] (%)
6	3	0.23	2.32
	4	0.31	3.08
	5	0.39	3.83
20	3	0.78	7.53
	4	1.04	9.93
	5	1.30	12.3
35	3	1.37	12.8
	4	1.82	16.8
	5	2.28	20.6

[a]Range 0.86–2.5; see text and References 2 and 11.
[b]Range in the literature; see text and Reference 13.
[c]Data for reported prevalence did not include length of time anesthesiologists were in practice, but the mean could be estimated to be approximately 10 yr in the prevaccine era (16,17).

Table 5. Risk of Hepatitis B Infection for Nonimmunized Surgeons Over a 10-Year Period, Assuming No Increase in Prevalence, 1000 Operating Room Hours, and an Average of 4.2 Needlesticks[a] Each Year

Seroconversion per parenteral exposure to infected blood[b] (%)	Infected patients in population[b] (%)	1-yr risk of infection (%)	10-yr risk of infection[c] (%)
6	3	0.76	7.31
	4	1.01	9.63
	5	1.26	11.9
20	3	2.52	22.5
	4	3.36	29.0
	5	4.20	34.9
35	3	4.41	36.3
	4	5.88	45.5
	5	7.35	53.4

[a]Range 3.8–6.2; see text and References 2, 4, and 10.
[b]Range in the literature; see text and Reference 13.
[c]Data for reported prevalence did not include length of time surgeons were in practice, but the mean could be estimated to be approximately 10 yr in the prevaccine era (13,16).

Discussion

The accuracy of our formula and estimates in the literature for the factors in the formula seem to be confirmed by the fact that the range we calculated for risk of hepatitis B infection for surgeons agrees with the actual reported rate of prevalence in the prevaccine era. Results of studies of the increased risk of hepatitis B infection with longer duration of exposure are conflicting (16,17). Such studies do not alter the validity of our formula; they simply increase the range of uncertainty when it is applied. Estimates for the risk of infection from a needlestick are only that—estimates. Crude though they may be, they are the best estimates to be obtained for both hepatitis B and HIV inoculae. The reported prevalence of hepatitis B among anesthesiologists is at the high end of our calculated range, possibly because of underestimation of the frequency of needlesticks or because needlestick injuries to anesthesiologists are of a riskier nature (more direct, fewer glancing). If so, the estimated risk of HIV infection for anesthesiologists would also be too low. The actual risk of HIV infection for anesthesiologists may be higher than our calculated range of 0.05%–4.50% over a 30-yr period in a population without change in HIV prevalence.

Table 6. One-Year Risk of Hepatitis B Infection for Nonimmunized Third-Year Medical Students, Assuming 1 or 5 Needlesticks[a] Each Year

Seroconversion per parenteral exposure to infected blood[b] (%)	Infected patients in population[b] (%)	1 Needlestick (%)	5 Needlesticks (%)
6	3	0.18	0.90
	4	0.24	1.20
	5	0.30	1.50
20	3	0.60	3.00
	4	0.80	4.00
	5	1.00	5.00
35	3	1.05	5.25
	4	1.40	7.00
	5	1.75	8.75

[a]Range 0–5; see text and References 2 and 12.
[b]Range in the literature; see text and Reference 13.

The risk of infection may not be higher for surgeons than for anesthesiologists. Actual risk may be less than that perceived for surgeons but higher than that perceived for anesthesiologists. Certain specialties of surgical practice may confer different risks than others, but such was not evident from the literature. We speculate that one explanation for miscalculation of risk for surgeons versus anesthesiologists may be that the two sustain different types of needlestick injuries. The glancing injuries surgeons experience during closure with sutures are often superficial and do not penetrate deeply. In contrast, injuries to anesthesiologists frequently involve direct needlestick punctures that penetrate deeply and represent greater exposure to blood or body fluids. Although surgeons may sustain more needlestick injuries than do anesthesiologists, their degree of exposure to infected blood or fluids may not be as great per exposure.

Medical students, who are inexperienced in performing common procedures such as drawing blood, are obvious candidates for accidental needlesticks and would be expected to sustain more such injuries than do surgeons or anesthesiologists. Jones (12) reported that 21% of 42 beginning fourth-year medical students at Cornell University had been stuck accidentally by a needle during their third year of medical school. Because applicability of results was limited by the small sample size of the study, more data need to be gathered to assess accurately the risks of HIV or hepatitis B infection to third-year medical students.

Although many studies report a low risk of HIV transmission from patient to physician (3–5), the potential for HIV infection still exists. Clearly, in the prevaccine era, the risk for infection with hepatitis B was greater than the risk for infection with HIV is now (compare Tables 1–3 with Tables 4–6); but the consequences of infection with hepatitis B are not perceived to be as devastating as are those for HIV infection. Our calculated risk of HIV infection for anesthesiologists over a 30-yr period ranges from 0.05% to 13.0%. Specific factors, however, influence and determine the actual degree of risk. For example, geographic location is important: a physician practicing where the prevalence of HIV-infected patients is reported at 0.32% faces a much lower risk (0.05%–0.22%) than the practitioner in an area where the prevalence rate is 23.6% (risk 4.5%–13.0%).

Physicians can decrease risk further by taking precautions to guard against exposure to blood and body fluids. For example, using two pairs of gloves increases protection against exposure, because the puncture rate is 1 to 12 times greater (average 5) when only one pair is used (19,20). The risks to anesthesiologists and surgeons over a 30-yr career range from 1 in 10,000 for someone following universal precautions and serving a low-risk population to 1 in 3 for someone not using precautions and serving a high-risk population. A risk of 1 in 100 is estimated for those anesthesiologists using precautions while serving a high-risk population. These risks are considerably greater than the yearly risk of fatality to other public health and safety officers, estimated at 1 in 4000 for a California police officer and 1 in 10,000 for a California firefighter (1,24).

The tables do not present ranges of risk within predetermined confidence limits; rather, they show the estimated risk in different geographic areas with and without the use of precautions. Studies have also shown that in the past, most health care professionals have not adhered strictly to precautions to prevent exposure to blood and body fluids (22). A substantial proportion of accidental exposures might have been avoided had such precautionary measures been taken. Through immunization, most anesthesiology and surgery residents have reduced their risk of hepatitis B infection since the survey periods cited (13,14,16–18). Although physicians face the risk of HIV infection, the extent and reduction of that risk depend on various factors. Physicians can and do lower risk when educated to follow safe procedures (22–28).

Our risk calculations are based on extrapolations from data involving other specialties. For example, although double gloving may decrease risk for glancing injuries sustained by surgeons during suturing (19,20), we do not know whether double gloving is equally as effective in decreasing the risk for the injuries commonly sustained by anesthesiologists during needle recapping. In fact, if double gloving induces clumsiness, it may indeed increase needlestick injuries. Further, the advisability of not recapping has not yet been tested—perhaps direct needlestick injuries to other medical personnel will be increased when practitioners discard an unrecapped needle.

Our calculations reveal that the occupational risk of HIV infection for anesthesiologists is not trivial. Still, the precise degree of risk protection provided by precautionary measures is not clear. Calculation of risk alone, however precise, may not be sufficient. We look forward to studies of the effectiveness of preventive measures for reducing risk of HIV infection to anesthesiologists. Such studies may be the best inducements for more complete compliance with precautionary procedures and, ultimately, for the greatest reduction in risk.

References

1. Mangione CM, Gerberding JL, Cummings SR. Occupational exposure to HIV: frequency and rates of underreporting of percutaneous and mucocutaneous exposures by medical housestaff. Am J Med 1991;90:85–90.
2. Heald AE, Ransohoff DF. Needlestick injuries among resident physicians. J Gen Intern Med 1990;5:389–93.
3. Allen JR. Health care workers and the risk of HIV transmission. Hastings Cent Rep 1988;18(April/May Suppl):2–5.
4. Lowenfels AB, Wormser GP, Jain R. Frequency of puncture injuries in surgeons and estimated risk of HIV infection. Arch Surg 1989;124:1284–6.
5. Centers for Disease Control. Public health service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. MMWR 1990;39(RR-1):1–14.
6. Kelen GD, Fritz S, Qaqish B, et al. Unrecognized human immunodeficiency virus infection in emergency department patients. N Engl J Med 1988;318:1645–50.
7. Gerberding JL, Littell C, Tarkington A, Brown A, Schecter WP. Risk of exposure of surgical personnel to patients' blood during surgery at San Francisco General Hospital. N Engl J Med 1990;322:1788–93.
8. Centers for Disease Control. Human immunodeficiency virus infection in the United States: a review of current knowledge. MMWR 1987;36(Suppl S-6):35.

9. Centers for Disease Control. HIV prevalence estimates and AIDS case projections for the United States: report based on a workshop. MMWR 1990;39(RR-16):1–31.
10. Hussain SA, Latif ABA, Choudhary AAAA. Risk to surgeons: a survey of accidental injuries during operations. Br J Surg 1988;75:314–6.
11. Maz S, Lyons G. Needlestick injuries in anaesthetists. Anaesthesia 1990;45:677–8.
12. Jones DB. Percutaneous exposure of medical students to HIV. JAMA 1990;264:1188–90.
13. Dienstag JL, Ryan DM. Occupational exposure to hepatitis B virus in hospital personnel: infection or immunization? Am J Epidemiol 1982;115:26–39.
14. Advisory Committee on Immunization Practices. Inactivated hepatitis B virus vaccine. MMWR 1982;31:317–28.
15. Schlech WF III. The risk of infection in anaesthetic practice. Can J Anaesth 1988;35:S46–51.
16. Denes AE, Smith JL, Maynard JE, Doto IL, Berquist KR, Finkel AJ. Hepatitis B infection in physicians. Results of a nationwide seroepidemiologic survey. JAMA 1978;239:210–2.
17. Berry AJ, Isaacson IJ, Kane MA, et al. A multicenter study of the prevalence of hepatitis B viral serologic markers in anesthesia personnel. Anesth Analg 1984;63:738–42.
18. Berry AJ, Isaacson IJ, Kane MA, et al. A multicenter study of the epidemiology of hepatitis B in anesthesia residents. Anesth Analg 1985;64:672–6.
19. Matta H, Thompson AM, Rainey JB. Does wearing two pairs of gloves protect operating theatre staff from skin contamination? BMJ 1988;297:597–8.
20. McLeod GG. Needlestick injuries at operations for trauma. Are surgical gloves an effective barrier? J Bone Joint Surg 1989;71-B:489–91.
21. Song ES, Stotka JL, Chinchilli VM, Williams DS, Stuart CG, Markowitz SM. Are universal precautions effective in reducing the number of occupational exposures among health care workers? A prospective study of physicians on a medical service. JAMA 1991;265:1123–8.
22. Stevens CK, Mentis SW, Downs JB. The human immunodeficiency virus: knowledge and precautions among anesthesiology personnel. J Clin Anesth 1991;3:266–75.
23. Roizen MF. Do old practice habits die hard? (Editorial). J Clin Anesth 1991;3:263–5.
24. Hermann RC. Risks of HIV exposure to medical students and health care personnel (Editorial). JAMA 1990;264:1187.
25. Schiff SJ. A surgeon's risk of AIDS. J Neurosurg 1990;73:651–60.
26. Howard RJ. Human immunodeficiency virus testing and the risk to the surgeon of acquiring HIV. Surgery 1990;171:22–6.
27. Orient JM. Assessing the risk of occupational acquisition of the human immunodeficiency virus. Implications for hospital policy. South Med J 1990;73:1121–7.
28. Berry AJ, Isaacson IJ, Hunt D, Kane MA. The prevalence of hepatitis B viral markers in anesthesia personnel. Anesthesiology 1984;60:6–9.

Coagulopathy After Reinfusion of Autologous Scavenged Red Blood Cells

David J. Murray, MD, Kurt Gress, MD, and Stuart L. Weinstein, MD

Departments of Anesthesia and Orthopedics, University of Iowa Hospitals and Clinics, Iowa City, Iowa

Cell scavenging techniques reduce homologous blood transfusion (1–5). Coagulopathy, one of the potential hazards of reinfusing scavenged autologous blood, is an infrequent occurrence when automated cell processing systems are used to collect, anticoagulate, and wash scavenged red blood cells (1–5). Bleeding problems associated with autologous red blood cell administration are believed to be primarily a result of dilutional rather than disseminated coagulopathy (6–9). When disseminated intravascular coagulopathy is observed during the reinfusion of scavenged autologous blood, concomitant problems such as shock and tissue trauma, rather than the autologous red blood cells per se, are the usual causes of the coagulopathy (6,7). We describe two patients who experienced disseminated coagulopathy after reinfusion of autologous scavenged red blood cells collected during elective surgery for scoliosis correction.

Case Report

Patient 1

A 12-yr-old, 22-kg boy with cerebral palsy and spastic quadripariesis required Harrington rod insertion for progressive scoliosis. There was no history suggestive of a bleeding disorder. A preoperative hematologic profile included a hematocrit of 40%, normal prothrombin time (PT), and activated partial thromboplastic time (aPTT) of 12 and 24 s, respectively (PT normal range 10–13 s, aPTT normal range 22–33 s), fibrinogen concentration of 340 mg/dL, and platelet count of 354,000/mm^3.

After an inhaled induction of anesthesia, the trachea was intubated. An intraarterial catheter and a urinary catheter were placed before prone positioning for the operative procedure. Anesthesia was maintained with halothane and nitrous oxide throughout the operative procedure. Crystalloid solutions were used as intravenous replacement fluids until blood loss was estimated at 600 mL and a hematocrit of 28% was recorded. The first unit of packed red cells was administered during the second hour of operation. At the conclusion of the third hour of operation, 2200 mL of crystalloid (0.9 NaCl and lactated Ringer's solution) and 2 U of packed red blood cells had been administered for an estimated blood loss of 1200 mL (Table 1). Monitoring of arterial blood pressure, urine output, and arterial blood gases throughout the 3-h operative procedure confirmed a stable hemodynamic situation with normal acid-base balance.

Surgical hemostasis was evaluated after blood loss was estimated at one blood volume. Minimal bleeding from wound edges and clot formation on the surgical field suggested that hemostasis was adequate, but because blood loss equaled one blood volume, a coagulation profile (PT, aPTT, fibrinogen level, and platelet count) was obtained. The clinical impression of adequate hemostasis was confirmed by the coagulation profile, which indicated a dilutional decrease in coagulation factors and platelets (PT 14 s, aPTT 29 s, fibrinogen level 160 mg/dL, platelet count 186,000/mm^3). The hematocrit was 30% (Table 1).

As wound closure was started, autologous red blood cells scavenged from the surgical field by means of a Hemonetics Cell Saver II system were processed for reinfusion. A plastic suction device with a heparinized saline solution added at the suction tip had been used to aspirate blood from the surgical field. Red blood cells (300 mL) collected during the 3-h operation were washed with 1500 mL of normal saline solution. After the wash and centrifuge cycle, 1 U of autologous packed red blood cells was administered over a period of 20 min by means of a filtered blood administration set. After autologous infusion, a marked increase in bleeding from the surgical field was noted. Wound edges previously hemostatic were minimally responsive to electrocautery. No clot formation was noted. At the same time,

Accepted for publication March 4, 1992.

Address correspondence to Dr. Murray, Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Summary of Blood Loss in Two Patients Undergoing Surgical Correction for Scoliosis

Time of sample	Estimated blood loss (mL)	Estimated blood volume loss	Fluid and blood replacement	Hematologic profile				
				Hematocrit (%)	PT (s) (normal range 10–12 s)	aPTT (s) (normal range 22–33 s)	Platelets (per mm^3)	Fibrinogen (mg/dL)
Patient 1. (12 yr, 22 kg, estimated blood volume 1500 mL)								
Preoperative (0 h)	0	0	0	40	12	24	354,000	283
Intraoperative (3 h)	1200	0.8	2 U pRBC	30	14	29	186,000	160
Hemoglobinuria and abnormal surgical hemostasis (3.6 h)[a]	1500	1.0	+ 400 mL autologous RBC	33	18	75	46,000	50
Immediate postoperative (5 h)	4000	2.7	4 U WB; 4 U FFP; 1 pheresed platelet (8 U)	32	16	48	69,000	170
Patient 2. (18 yr, 30 kg, estimated blood volume 2100 mL)								
Preoperative (0 h)	0	0	0	36	12	28	235,000	340
Intraoperative (3 h)	2400	1.2	4 U pRBC	31	13	35	140,000	160
Hemoglobinuria and abnormal surgical hemostasis (3.8 h)[a]	3000	1.5	+ 600 mL autologous RBC	28	20	>150	19,000	19
Immediate postoperative (6 h)	5000	2.5	4 U FFP; 2 U pRBC; 2 U WB; 1 pheresed platelet (8 U)	30	15	35	94,000	160

pRBC, packed red blood cells; RBC, red blood cells; PT, prothrombin time; aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; WB, whole blood.
[a] Coagulation tests obtained after increased blood loss on surgical field.

red urine was noted in the urimeter. A centrifuged blood sample confirmed hemoglobin in the plasma. The blood bank was alerted of a possible transfusion reaction, and blood for a plasma hemoglobin, repeat cross-match, as well as PT, aPTT, platelet count, and fibrinogen level, was sent to the laboratory. Blood for coagulation tests was obtained 40 min after the previous coagulation profile (Table 1). Despite continued bleeding, surgical drains were placed, wound closure was completed, and a pressure dressing was applied. The patient was taken to the recovery room, where the trachea remained intubated and ventilation remained controlled.

Coagulation results obtained at the onset of increased bleeding confirmed coagulopathy (PT 18 s, aPTT 75 s, fibrinogen level 50 mg/dL, platelet count 46,000/mm^3, plasma hemoglobin 110 mg%) (Table 1). Additional crystalloid was administered intravenously in the recovery room while awaiting platelets, fresh-frozen plasma, and blood from a repeat cross-match. With persistent bleeding from surgical drains, blood-saturated dressings, and a hematocrit of 15%, the patient was returned to the operating room for reexploration of the wound. Over the course of the next 90 min, a single-donor platelet unit (equivalent to eight single adult platelet units), 4 U of whole blood, and 4 U of fresh-frozen plasma were administered. Diffuse microvascular bleeding from the surgical site gradually abated. The wound was closed and the patient was transferred to the intensive care unit. A hematology and coagulation profile on arrival in the pediatric intensive care unit indicated a PT and aPTT of 16 and 48 s, respectively, and a platelet count of 69,000/mm^3 and fibrinogen level of 170 mg/dL. Hematocrit was 32% (Table 1). In vitro cross-matches of all donor units transfused were compatible with the recipient, and Coomb's testing was negative. Scant sanguineous drainage from drains changed to serous drainage over the next 24-h period. The trachea was extubated the following morning, and the patient spent the next 48 h in the intensive care unit. Over the next 36 h, coagulation tests became normal. Repeat coagulation tests during a 10-day hospital stay were normal. On postoperative day 20, the patient was discharged from the hospital.

Patient 2

An 18-yr-old, 30-kg male patient with a history of myelomeningocele and a T-10 sensory level required posterior spinal stabilization for progressive scoliosis. This patient's history was negative for a bleeding disorder. Previous orthopedic and urologic surgery had been uncomplicated. Preoperative coagulation tests were normal (PT 12 s, aPTT 28 s, platelet count

235,000/mm^3). A preoperative hematocrit was 36%, and fibrinogen level was 283 mg/dL.

After intravenous induction of anesthesia with thiopental, anesthesia was maintained with nitrous oxide and isoflurane. After tracheal intubation, a radial artery catheter and urinary catheter were placed before positioning the patient prone for the operative procedure. During the operation, a Hemonetics Cell Saver II was used to collect blood from the operative field. The autologous cells were mixed with a dilute heparin solution and aspirated to a filtered reservoir by means of a plastic suction device.

Over the initial 3 h of operation, intravenous fluid replacement had included 2500 mL of crystalloid and 4 U of packed red blood cells for blood loss estimated at 2.0 L. Arterial blood pressure, urine output, repeated analysis of arterial blood gases, and serial hematocrits indicated a stable intraoperative course. Surgical hemostasis was judged adequate, but because blood loss was more than one blood volume, coagulation tests were obtained. A PT and aPTT of 13 and 35 s, respectively, platelet count of 140,000/mm^3, and fibrinogen level of 160 mg/dL were reported 30 min later (Table 1).

The operative procedure was close to completion. Autologous red blood cells, 600 mL collected during the operation, were processed by washing and centrifuging the scavenged cells with 2 L of normal saline solution. The scavenged red blood cells were then reinfused by means of a filtered blood administration set. Fifteen minutes later, red urine was noted. Coincidentally, surgical bleeding increased. The absence of clot formation and persistent microvascular bleeding despite the use of electrocautery and suture ligation suggested coagulopathy. Blood for a plasma hemoglobin, coagulation profile, and repeat cross-match were sent to the laboratory. A PT and aPTT of 20 s and >150 s, respectively, fibrinogen level of 19 mg/dL, and platelet count of 19,000/mm^3 were reported 40 min later (Table 1); the hematocrit was 28%. Plasma hemoglobin and fibrin degradation products reported 3 h later were 94 mg/dL and >40, respectively. Two units of fresh-frozen plasma, an additional 2 U of packed red blood cells, and a single-donor pheresed platelet unit were administered, but increased bleeding persisted. An additional 2 U of fresh-frozen plasma and 2 U of whole blood were administered over the next 90 min for continued microvascular bleeding. Clinical hemostasis gradually improved with this therapy, wound closure was completed, and the patient was transferred to the intensive care unit. The hematologic and coagulation profile on arrival in intensive care indicated a hematocrit of 30%, PT of 15 s, aPTT of 35 s, platelet count of 94,000/mm^3, and fibrinogen level of 160 mg/dL. A repeat cross-match was negative, and no red blood cell antibodies were detected on a repeat antibody screen.

An additional unit of packed red blood cells was administered during the 48 h the patient remained in intensive care. The hemoglobinuria cleared in the first 4 h postoperatively. The PT and aPTT were normal by the second postoperative day without additional coagulation factor replacement. Platelet count returned to normal over the next 72 h.

Discussion

Disseminated coagulopathy is difficult to differentiate from dilutional coagulopathy in situations of major blood loss without in vitro hemostatic test results (10–12). After one blood volume loss, hemostasis was judged adequate in both patients, and coagulation profiles indicated a dilutional decline in platelets and coagulation factors (10). Abnormal surgical hemostasis became apparent after autologous red blood cell infusion. The temporal relation among infusion of autologous cells, hemoglobinuria, increased microvascular bleeding, and in vitro coagulation test changes suggests that autologous red blood cells led to coagulopathy. The marked decline in platelet count, fibrinogen level, and prolongation of PT and aPTT, in association with a relatively small volume of autologous cells, suggests disseminated, rather than dilutional, coagulopathy (10,13). If a hemolytic transfusion reaction caused the coagulopathy, repeat cross-matching and screening for red blood cell antibodies would probably have detected the problem. If inadequate tissue perfusion had been the cause of the coagulopathy, an unstable intraoperative course, suggested by arterial blood pressure measurements, acidosis, hypoxia, or oliguria, would have been expected during the perioperative period.

Red blood cells obtained from intraoperative scavenging techniques have been cited as a potential trigger for coagulopathy, but in most laboratory and clinical settings, multiple blood volume exchange is required before the development of a coagulopathy (6–9). A recheck of the scavenging system in both patients confirmed that proper suctioning, appropriate concentrations of heparin, and suitable type and volume of wash solutions (normal saline solution) were used to aspirate, wash, and centrifuge red blood cells in both patients (14,15). Scavenged red blood cells should be aspirated from the surgical field at the lowest possible suction power. In both patients, suction power was maintained at 300 mm Hg throughout red blood cell scavenging (a suction level at the upper limit recommended by manufacturers). In addition, red blood cells were washed in both patients with five times and three times the volume of normal saline solution, respectively, rather than six

times the volume of red blood cells recommended for orthopedic procedures (14,15). Perhaps a combination of too vigorous suction, inadequate wash cycle, and red blood cell damage during surgical dissection contributed to hemoglobinuria and coagulopathy in both patients.

These two patients illustrate the potential for disseminated coagulopathy after reinfusion of even a small volume of washed scavenged red blood cells. Activation of coagulation by damaged erythrocytes or by mediators released by platelets or leukocytes is the probable cause of coagulopathy (13,16,17). Autologous erythrocyte stroma can act as thromboplastin, initiating disseminated coagulopathy in animal models (18,19). A similar mechanism is believed to be partially responsible for the coagulopathy of immunologically mediated hemolytic transfusion reactions (19). The hemoglobinuria and elevated plasma hemoglobin indicate that the reinfused red blood cell concentrate contained damaged red blood cells and perhaps other debris that could act as thromboplastinlike substances and initiate disseminated coagulation. Bull and Bull (16) described a salvaged blood syndrome but only in patients who required major vascular surgery. In vivo animal studies suggest "mechanochemical" activation of platelets and leukocytes can cause disseminated coagulopathy (13,17). The presence of hemoglobinuria in our two patients who had orthopedic surgery suggests a different mechanism of coagulopathy than in the patients identified by Bull and Bull (16) with "salvaged blood syndrome."

In dilutional coagulopathy, clinical hemostasis remains normal until more than one blood volume has been replaced by packed cells (10). Abnormal surgical hemostasis gradually develops until coagulation factor replacement is indicated (10,11). In contrast, disseminated coagulopathy often develops rapidly, and multiple blood components may be required to achieve effective surgical hemostasis (11,12). These two patients illustrate the multiple blood components that are required when disseminated coagulopathy is the cause of abnormal hemostasis.Although coagulation tests helped establish the diagnosis of disseminated coagulopathy, fresh-frozen plasma, platelet concentrates, and whole blood were titrated until surgical hemostasis improved, as judged by clot formation and decreased microvascular bleeding. Despite the presence of adequate surgical hemostasis in the perioperative period, in vitro coagulation test abnormalities persisted in the postoperative period in both patients.

During posterior spinal stabilization surgery, patients with osteopenic bone secondary to neuromuscular disease have greater operative blood loss than patients with idiopathic scoliosis (20). In both of our patients, increased bone and tissue debris may have been aspirated during autologous scavenging, and, theoretically, more coagulation factor activation and red blood cell damage are possible during operation (20,21). In 1982, Flynn et al. (1) reported decreased homologous transfusion requirements when intraoperative scavenging techniques were used during orthopedic surgical procedures, but 5 of 97 (5%) patients experienced transient hemoglobinuria without coagulopathy. When autologous red blood cell scavenging is utilized in orthopedic procedures, the wash cycle is believed to be effective in the removal of tissue debris and hemolyzed red cells (14,15), but as these two patients illustrate, washing may not prevent coagulopathy. The limited yield of autologous scavenging techniques and the bleeding complications in these two patients led us to discontinue the practice of autologous scavenging in patients with severe neuromuscular disease and osteopenic bone who require major spinal surgery. Whether our decision applies to other institutions remains to be determined.

References

1. Flynn JC, Metzger CR, Csencsitz TA. Intraoperative autotransfusion (IAT) in spinal surgery. Spine 1982;7:432–5.
2. Jones RB, Propst-Procter SI, McDougall IR, et al. Erythrocyte survival following intraoperative autotransfusion in orthopaedic surgery. Orthop Trans 1984;8:38.
3. Winter WG, Huene DCR, Touton CH, et al. Autologous transfusion in orthopaedic surgery. Contemp Orthop 1982;5: 77–81.
4. Kruger IM, Colberg JM. Intraoperative autologous transfusions in children undergoing spinal surgery. J Pediatr Orthop 1985;5:330.
5. Keeling MM, Gray LA Jr, Brink MA, Hillerich VK, Bland KI. Intraoperative autotransfusion: experience in 725 consecutive cases. Ann Surg 1983;197:536–40.
6. Hauer JM, Thurer RL. Controversies in autotransfusion. Vox Sang 1984;46:8–12.
7. Moore EE. Letter to the editor. J Trauma 1981;21:824.
8. Bell WR. Hematologic aspects of autotransfusion. In: Hauer JM, Thurer RL, eds. Autotransfusion. New York: Elsevier, 1981:90–106.
9. Stillman RM, Wreziewicz WW, Stanczewski B, et al. The haemotological hazards of autotransfusion. Br J Surg 1976;63: 651.
10. Murray DJ, Olson J, Strauss R, Tinker JH. Coagulation changes during packed red cell replacement of major blood loss. Anesthesiology 1988;69:839–45.
11. Ciaverella D, Reed RL, Counts RB, et al. Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. Br J Haematol 1987;67:365–8.
12. Miller RD. Transfusion therapy. In: Miller RD, ed. Anesthesia. 3rd ed. New York: Churchill Livingstone, 1990:1476–81.
13. Bull BS, Bull MH. Enhancing the safety of intraoperative RBC salvage. J Trauma 1989;29:320–5.
14. Raines J, Bluth J, Brewster JC, Darling RC. Intraoperative autotransfusion equipment, protocol and guidelines. J Trauma 1976;16:616–23.
15. Stehling LC, Zauder HL, Rogers W. Intraoperative autotransfusion. Anesthesiology 1975;43:337–45.

16. Bull BS, Bull MH. The salvaged blood syndrome: a sequel to mechanochemical activation of platelets and leucocytes? Blood Cells 1990;16:5–25.
17. Bull MH, Bull BS, VanAusdell GS, Smith LL. Clinical implications of procoagulant and leukoattractant formation during intraoperative salvage. Arch Surg 1988;123:1073–8.
18. Birndorf N, Lopez H. Intravascular coagulation in anomologous monkeys produced by red cell stroma. Clin Res 1970;18: 398.
19. Goldfinger D. Acute hemolytic transfusion reactions: a fresh look at pathogenesis and considerations regarding therapy. Transfusion 1977;17:85–98.
20. Bobechko WK. Blood loss in spinal surgery: state of the art review. Spine 1991;5:75–82.
21. Dorang LA, Klebanoff G, Kemmerer WT. Autotransfusion in long-segment spinal fusion: an experimental model to demonstrate the efficacy of salvaging blood contaminated with bone fragments and marrow. Am J Surg 1972;123:686–8.

Accidental Overdose of Systemic Morphine During Intended Refill of Intrathecal Infusion Device

Christopher L. Wu, MD, and Richard B. Patt, MD

Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, Rochester, New York

Intrathecal morphine is an effective and well-recognized method of alleviating intractable pain in cancer patients (1,2). Several implantable systems have been developed to facilitate delivery of opioids on a long-term basis (3). Some of these devices incorporate a drug reservoir to eliminate the need for frequent injections and externalized hardware. When refilling the reservoir, there is the potential for a misplaced injection of a relatively large dose of opioid. This may occur despite the presence of alarm features. This report describes a case of an accidental massive, nonfatal overdose of subcutaneous morphine that occurred in the course of refilling the reservoir of a Medtronics Synchromed infusion pump.

Case Report

A 64-yr-old woman (weight 57 kg, height 164 cm) underwent implantation of a Medtronics Synchromed infusion pump (Figure 1) with an intrathecal catheter and was scheduled for a follow-up visit to refill the pump reservoir 12 days postoperatively. The patient had a history of widely metastatic renal cell carcinoma resulting in severe lumbar pain that was poorly controlled with oral pharmacotherapy (sustained-release morphine, 90 mg three times a day; Percocet, 2 tablets every 3 h, as needed) but had responded well to intermittent doses of intrathecal morphine.

The staples over the incision were removed, and a telemetry unit was activated over the infusion device, which was determined to be functioning correctly. The area over the device was cleansed with Betadine and was draped in a sterile fashion. The outline of the reservoir was palpated, and its center was pierced with a 22-gauge noncoring (Huber) needle. A characteristic "give" thought to correlate with puncture of the device's silicone septum was perceived. Three milliliters of slightly blood-tinged fluid was aspirated, and 18 mL of morphine (25 mg/mL) was injected without difficulty through the needle. Small volumes of slightly blood-tinged fluid were aspirated twice during the injection. The infusion device was reset by means of the telemetry unit to a setting reflecting that it was replenished. After a brief period of observation, the patient was discharged.

Approximately 2 h later, the patient's husband telephoned and reported that his wife had become increasingly confused and lethargic and was unable to ambulate. The patient's spouse was instructed to bring the patient immediately into the clinic. On arrival, arterial blood pressure was 156/82 mm Hg, with a heart rate of 100 beats/min. Respirations were 12 breaths/min and color was normal. She was disoriented as to place and time but denied having any pain. Normal saline solution was infused through an intravenous cannula, and naloxone (0.16 mg) was administered in two divided doses. The patient became markedly more responsive, alert, and oriented, and respiratory rate increased to 16 breaths/min.

After 1 h of observation, the patient was transferred to the emergency room for further monitoring. Continuous pulse oximetry and electrocardiogram were applied. Oxygen saturation remained >95%, and normal sinus rhythm was maintained. Vital signs were recorded every hour, and the staff was informed to notify the emergency room physician of respiratory rates <12 breaths/min. The patient was further assessed by measures of pupillary size and reaction (increasing from 2 mm and sluggish to 4 mm and reactive by discharge), extremity strength (increasing from 3/5 to 5/5), and Glasgow coma scale (increasing from 13 to 15). Arterial blood gas levels were not obtained. Additional doses of naloxone were not administered.

The drug reservoir was refilled in the emergency room the following morning. The skin over the device was prepped and draped in a routine sterile fashion. The outline of the reservoir was palpated, and the center of the pump was pierced with a

Accepted for publication March 11, 1992.

Address correspondence to Dr. Patt, University of Rochester Medical Center, Department of Anesthesiology, Box 604, 601 Elmwood Avenue, Rochester, NY 14642.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

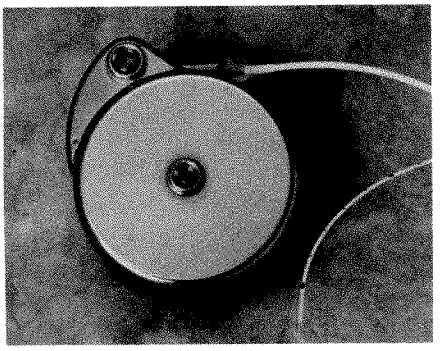


Figure 1. Medtronics Synchromed infusion pump, a totally implantable drug infusion device suitable for the administration of opioid analgesics into the epidural or intrathecal space. The hockey puck-sized microcircuitry-controlled pump is usually implanted within the subcutaneous tissue of the abdomen. The 18-mL capacity reservoir of the device permits the drug supply to be replenished intermittently (1–2 mo). The portal that is utilized to intermittently replenish the pump reservoir is located in the center of the device. An accessory portal that bypasses the pump circuitry, permitting direct access to the central nervous system is located near the periphery of the device and is used for myelography and the administration of supplemental bolus injections. A portable lap-top computer is utilized to alter infusion rate, and a programming wand transmits new information to the infusion device noninvasively by telemetry.

22-gauge noncoring (Huber) needle. A 20-mL syringe was filled with 18.0 mL of morphine (25.0 mg/mL). An initial injection of 3 mL was aspirated in its entirety and was observed to be colorless. A further 10-mL injection was also easily aspirated and was also observed to be clear. Finally, the entire 18-mL solution was injected through the needle without difficulty. The infusion pump was reset to read a reservoir volume of 18.0 mL containing morphine (25.0 mg/mL) infusing at a rate of 0.2 mg/h, with the low-battery alarm enabled at 2.0 mL. The patient was subsequently discharged without further problems and with maintenance of excellent analgesia.

Discussion

Accidental overdose of morphine in the course of refilling an intrathecal infusion device is an uncommon event but has been known to occur (personal communication, Medtronics, August 26, 1991). The potential for accidental overdose owing to equipment malfunction or human error has been cited as a possible disadvantage of implantable systems (3). Accidental massive overdoses of opioids have been reported in other settings, including malfunction of a patient-controlled analgesia device (administration of 495 mg of meperidine within 20 min, resulting in respiratory arrest) (4) and with epidural (5) and intrathecal morphine (6). Independent of route of administration, excessive doses of opioids may result in a variety of adverse outcomes, including hypothermia, myoclonic seizures, pulmonary edema, respiratory depression, coma, and death (7,8).

In this case, a patient accidentally received a subcutaneous bolus injection of 480 mg of morphine that had been intended to be instilled into the reservoir of an infusion pump and administered continuously over 6–8 wk. This event was manifested by disorientation, mild respiratory depression, and failure of locomotion, but no significant cardiovascular effects or lasting neurologic deficits resulted. Adverse effects were readily reversed with minute doses of naloxone. The relatively innocuous outcome was probably related to a constellation of factors, including opioid tolerance, early recognition, and prompt management. Given the patient's stable course, the emergency medicine housestaff were reluctant to believe that such an overdose actually occurred, but tolerance to high doses of opioids in patients chronically exposed to these drugs is well known in the cancer pain literature (9). Reversal of respiratory depression with an opioid antagonist is warranted in such cases, but this should be accomplished with small incremental doses to avoid the severe hypertension, dysrhythmias, and pulmonary edema that are presumably a result of the rapid increases in sympathetic tone that may accompany the sudden return of pain when opioid effects are antagonized too rapidly (10).

The Medtronics Synchromed infusion pump is a titanium device about the size of a hockey puck that is usually implanted within the subcutaneous tissue of the flank. Located within the center of the ventral surface of the pump is a small silicone injection port that must be palpated through the intact skin. Identification of the septum may be somewhat difficult shortly after surgery owing to swelling and inflammation. Passage of a 22-gauge eccentric tipped needle is marked by a characteristic yielding sensation and the easy return of clear fluid. In this case, postoperative edema prevented easy palpation of the port, and the curved tip of the Huber needle must have slid over the metal surface of the pump, mimicking the anticipated "give." The initial aspirations of mildly blood-tinged fluid may have originated from a seroma or resolving hematoma. Serous extravasations or seromas have been noted to be one of the most common complications after surgery on subcutaneous tissue (11). In most cases, serous fluid is clear but may be cloudy or blood-tinged. The possibility of bloody cerebrospinal fluid as the source of the aspirate is remote, but it should be noted that the most recent model of the Medtronic infusion pump has an (eccentric) side port that bypasses the reservoir (Figure 1). The entire dose injected into this side port would be administered intrathecally and would probably be lethal.

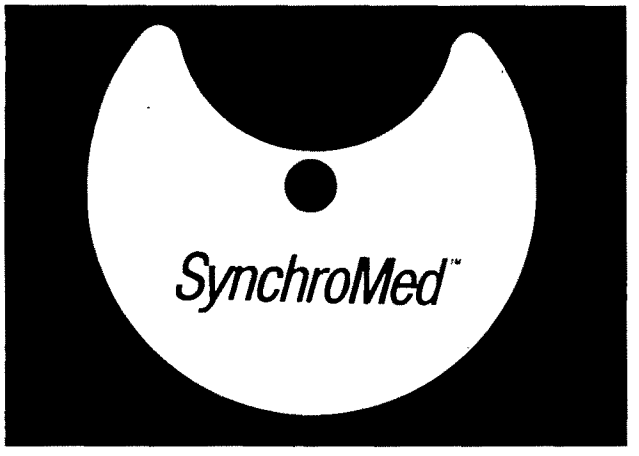


Figure 2. Circular plastic template provided by Medtronics as an adjunct to refilling the pump reservoir. The diameter of the template is identical to that of the pump, and its center orifice corresponds to the pump injection port.

The incidence of accidentally injecting outside the port and reservoir may be decreased by several means. Medtronics provides a circular template that is the same diameter as the pump and is distinguished by an orifice in its center that corresponds to the injection port (Figure 2). This device should be used as an adjunct to refilling the pump reservoir. In addition, injection and aspiration of small amounts of morphine solution (e.g., 3–5 mL) before administration of the entire dose may help confirm correct placement of the needle inside the reservoir. The entirety of the injected solution should be readily aspirated and should be colorless. This procedure can be repeated with gradually increasing volumes of injectate. If suspicion exists that the aspirated fluid is not morphine, a sample of the aspirate can be tested with a reagent strip that will determine the presence of glucose and protein, findings that would suggest, respectively, that cerebrospinal fluid or a seroma or resolving hematoma have been aspirated.

In summary, this report documents a case in which 480 mg of morphine was accidentally injected subcutaneously while refilling the reservoir of an infusion pump attached to an implantable intrathecal catheter. Mild respiratory depression and confusion developed approximately 2 h afterward. The patient was treated with 0.16 mg of naloxone intravenously. After 20 h of observation, the patient was discharged without sequelae. Several methods to decrease the incidence of such an injection are proposed.

References

1. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
2. Krames ES, Gershow J, Glassberg A, et al. Continuous infusion of spinally administered narcotics for the relief of pain due to malignant disorders. Cancer 1985;56:696–702.
3. Waldman SD, Coombs DW. Selection of implantable narcotic delivery systems. Anesth Analg 1989;68:377–84.
4. Kreitzer JM, Kirschenbaum LP, Eisenkraft JB. Safety of PCA devices. Anesthesiology 1989;70:881.
5. Dahl JB, Jacobsen JB. Accidental epidural narcotic overdose. Anesth Analg 1990;70:321–2.
6. Kaiser KG, Bainton CR. Treatment of intrathecal morphine overdose by aspiration of cerebrospinal fluid. Anesth Analg 1987;66:475–7.
7. Parkinson SK, Bailey SL, Little WL, Mueller JB. Myoclonic seizure activity with chronic high-dose spinal opioid administration. Anesthesiology 1990;72:743–5.
8. Bruera E. Narcotic-induced pulmonary edema. J Pain Symptom Management 1990;5:55–8.
9. Ventafridda V, Spoldi E, Caraceni A, De Conno F. Intraspinal morphine for cancer pain. Acta Anaesthesiol Scand 1987; 31(Suppl 85):47–53.
10. Flacke JW, Flacke WE, Williams GD. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. Anesthesiology 1977;47:376–8.
11. Gurdin MM, Carlin GA. Aesthetic surgery of the breast. In: Masters FW, Lewis JR, eds. Symposium on aesthetic surgery of the face, eyelid, and breast. Volume 4. St. Louis: Mosby, 1972:160.

Unsuccessful Interpleural Analgesia in a Patient With Mesothelioma

Zef A. Abraham, MD

Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

Interpleural analgesia is a method of pain control for acute and chronic pain conditions. The technique was first described as treatment for the acute postoperative pain after cholecystectomy or breast or renal surgery (1,2). The method has since been adapted for the relief of chronic pain syndromes of thoracic (3) and nonthoracic (4) origin. The present case report involves a patient with chest wall pain secondary to mesothelioma, refractory to interpleural analgesia. This difficulty has not been reported previously in a patient with mesothelioma.

Case Report

A 63-yr-old man with left-sided mesothelioma and associated chest wall pain was referred to our Center for Pain Management for assistance with pain control. The mesothelioma was attributed to long-term exposure to asbestos when the patient was a nuclear submarine builder, and the diagnosis was confirmed by computed tomography scan, which revealed a dense, loculated mass in the left pleural space and lung. A fluid sample revealed material consistent with mesothelioma. Neither surgery nor chemotherapy nor radiation therapy, according to our pulmonary medicine department, was likely to alter the outcome of the disease. Pain management was considered the primary objective of treatment, which at the time of referral consisted of oxycodone (10 mg) in combination with acetaminophen (650 mg) taken as often as every 3 h. This treatment resulted in lethargy without any significant degree of pain relief. The pain involved the left lateral and posterior chest at about T-7 to T-9 and was described as constant and throbbing. It was not exacerbated by respiratory movements or coughing.

Physical examination revealed a nondebilitated man, not in severe distress. His height was 180 cm, and he weighed 83 kg. Auscultation of the right hemithorax was without wheezes, rales, or rhonchi; the left hemithorax revealed markedly decreased breath sounds. Chest radiograph revealed volume loss of the left hemithorax with pleural thickening and effusion. Pulmonary function tests indicated a mild to moderate restrictive ventilatory defect with a mild reduction in diffusing capacity for carbon monoxide. Past medical history was otherwise significant for hiatal hernia controlled with ranitidine and mild hypertension well controlled with prazosin. There were no drug allergies.

The patient preferred a limited number of invasive procedures and minimal opiate intake. He was reluctant to ingest nonsteroidal antiinflammatory drugs owing to the presence of hiatal hernia. The patient agreed to a trial of interpleural analgesia, with the understanding that long-term catheter placement might be necessary.

With the patient in the right lateral decubitus position, an interpleural catheter was placed in the eighth intercostal space 10 cm from the posterior midline with a 17-gauge Tuohy needle with use of the loss-of-resistance technique as described previously by Reiestad and Stromskag (2). After negative aspiration, antibiotic ointment was applied, a plastic occlusive dressing was placed, and the catheter was taped over the left shoulder. The patient was then placed in the supine position, and 40 mL of 0.25% bupivacaine was instilled over 10 min. A continuous infusion of 0.25% bupivacaine at 10 mL/h was started. The patient noted a significant decrease in chest pain and no respiratory difficulties. His vital signs remained stable, and there were no changes in auscultation compared with the markedly decreased left-sided breath sounds before the procedure. Chest radiograph revealed a small left pneumothorax and significant left pleural effusion with a new air-fluid level. The patient was admitted to the inpatient unit as previously arranged, and the chest radiograph was repeated 6 h later. It revealed a 1-cm increase of the pleural effusion with no change in size of the pneumothorax. The new pleural effusion with air-fluid

Accepted for publication March 31, 1992.

Address correspondence to Dr. Abraham, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, P.O. Box 3333, New Haven, CT 06510.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

level was estimated to be of approximately the same amount (120 mL) as the bupivacaine infused. At this time, the left-sided chest wall pain returned. It exhibited the same characteristics as before the procedure. The local anesthetic infusion was discontinued, and pulmonary medicine evaluation was obtained. Needle thoracentesis was attempted but was unsuccessful owing to the loculated nature of the pleural effusion. Ultrasound-guided thoracentesis was decided against because the patient continued to be without respiratory distress. The interpleural catheter was removed, and the patient continued to have no respiratory distress. The left-sided chest wall pain had returned to baseline, and the chest radiograph was unchanged. The patient was discharged and sent home 48 h after initial placement of the interpleural catheter. Chest radiograph 6 wk later showed resolution of the air-fluid level, with return of the pleural effusion to baseline and resolution of the pneumothorax.

The patient subsequently underwent thoracic epidural neurolysis 8 wk after the interpleural analgesia, with 6 mL of 6% phenol at T-8 to T-9 under fluoroscopic guidance. He continued to be relatively pain free 6 mo after the epidural therapy.

Discussion

Mesothelioma is a tumor arising from epithelial and mesenchymal elements of the mesothelium. Approximately 65% of these tumors involve the pleura, 25% the peritoneum, and 10% the pericardium (5). Mesotheliomas are usually malignant and are associated with a history of asbestos exposure in at least 80% of cases (6). Chest pain is a common presentation and is generally nonpleuritic, aching, and frequently referred to the upper abdomen or shoulder (7). Chest radiograph indicating a large pleural effusion without either a meniscus or contralateral shift of mediastinal structures is typical of mesothelioma. The prognosis is poor. There is presently no satisfactory treatment, and median survival time after diagnosis ranges from 4 to 12 mo.

Interpleural analgesia was chosen for this patient because he was not satisfied with the analgesia and the side effects of opioids, was reluctant to ingest nonsteroidal antiinflammatory medications owing to the presence of hiatal hernia, and preferred a limited number of invasive procedures. The patient was aware that neuroablative techniques or epidural opioids could be used if the interpleural analgesia failed.

Fineman (3) described a patient with chronic pain secondary to bronchogenic carcinoma with unilateral pleural metastases and chest wall involvement who was successfully treated for 7.5 wk with interpleural analgesia. He reported that interpleural local anesthetic was successful despite extensive fibrosis and pleural thickening.

Mesothelioma typically spreads rapidly along the pleural surfaces. Eventually, the entire visceral and parietal pleural surfaces are infiltrated by a continuous layer of tumor (7). Pleural effusion is often present, and in this particular patient it was loculated. It has been suggested that the mechanisms of interpleural analgesia involve diffusion of local anesthetic from the interpleural space through the parietal pleura to as many as four sites of action: (a) multiple segmental intercostal nerve block (1); (b) the sympathetic chain (8); (c) the brachial plexus (9); and (d) splanchnic nerve block (4). This author believes that the presence of loculated pleural effusion prevented the local anesthetic from reaching the appropriate neural elements. Evidence for a barrier to absorption of the local anesthetic is the increasing size of the pleural effusion as the bupivacaine was infused. The estimated amount of the new pleural effusion with air-fluid level (120 mL) was approximately the same as the amount of bupivacaine infused. The initial 6 h of pain relief, followed by inadequate analgesia subsequent to an initial large bolus dose of 40 mL of 0.25% bupivacaine and then a continuous infusion of 0.25% bupivacaine at 10 mL/h, may be accounted for by sufficient concentration of drug with the initial bolus dose, followed by insufficient concentration in the pleural space when only 10 mL/h was mixed with the effusion fluid present. Perhaps a more concentrated bupivacaine solution, for example, 0.5%, would have been effective in overcoming the pleural pathology as a barrier to absorption, as might have been a higher rate of infusion or a repeat bolus dose of bupivacaine.

The small pneumothorax present after placement of the interpleural catheter is unlikely to have contributed to the ineffectiveness of the local anesthetic. Pneumothorax may be a deterrent to successful interpleural analgesia because the air space formed between the parietal and visceral pleurae may prevent adequate spread of local anesthestic. However, in this case it is thought to have contributed little to the inadequacy of interpleural analgesia because the patient initially had 6 h of satisfactory pain relief despite the presence of a small pneumothorax, which did not increase in size. However, the pleural effusion with air-fluid level did increase in an amount estimated to be equivalent to the bupivacaine infused.

In summary, a case of chest wall pain due to mesothelioma is presented that was unsuccessfully treated with interpleural analgesia. It is proposed that tumor involvement of the pleural surfaces and the loculated pleural effusion rendered the appropriate neural structures inaccessible to the local anesthetic. Therefore, the use of interpleural analgesia for the

chest wall pain of mesothelioma cannot be recommended.

References

1. Kvalheim L, Reiestad F. Interpleural catheter in the management of postoperative pain (abstract). Anesthesiology 1984;61: 3A.
2. Reiestad F, Stromskag KE. Interpleural catheter in the management of postoperative pain: a preliminary report. Reg Anaesth 1986;11:89–91.
3. Fineman SP. Long-term post-thoracotomy cancer pain management with interpleural bupivacaine. Anesth Analg 1989;68: 694–7.
4. Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. Anesth Analg 1988;67:479–81.
5. Antman KH. Clinical presentation and natural history of benign and malignant mesothelioma. Semin Oncol 1981;8:313–20.
6. Balmes J, Cullen MR, Matthay RA. Occupational and environmental lung disease. In: George RB, Light RW, Matthay MA, Matthay RA, eds. Chest medicine: essentials of pulmonary and critical care medicine. 2nd ed. Baltimore: Williams & Wilkins, 1990:277–306.
7. Light RW. Diseases of the pleura, mediastinum, chest wall and diaphragm. In: George RB, Light RW, Matthay MA, Matthay RA, eds. Chest medicine: essentials of pulmonary and critical care medicine. 2nd ed. Baltimore: Williams & Wilkins, 1990;381–412.
8. Morrow JS, Squier RC. Sympathetic blockade with interpleural analgesia (abstract). Anesthesiology 1989;71:A662.
9. Reiestad F, McIlvaine WB, Kvalheim L, Stokke T, Pettersen B. Interpleural analgesia in treatment of upper extremity reflex sympathetic dystrophy. Anesth Analg 1989;69:671–3.

Upper Airway Obstruction and Infant Botulism

Andrew Oken, MD, Steven Barnes, MD, Peter Rock, MD, and Lynne Maxwell, MD

Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland

The diagnosis of the etiology of acute upper airway obstruction (UAO) presents difficulties in infants but is important as any coexisting disease may itself be fatal. Guidelines for identification and management of UAO have been defined (1–3) and include multispecialty evaluation and carefully controlled operating room care. While urgently addressing a critical airway, the broad differential diagnosis of UAO must be considered (4). We present a case of acute UAO, first thought to be epiglottitis, in a patient who subsequently was found to have infant botulism. This is the first case report of botulism mimicking epiglottitis and causing acute UAO.

Case Report

A previously healthy 5-mo-old boy with no significant past medical or past surgical history presented to the emergency room with lethargy, drooling, increased irritability, and decreased oral intake of 3-day duration. He had been treated at another hospital for a presumed otitis media and tonsillitis with intramuscular ceftriaxone and oral amoxicillin. On arrival he was listless and had severe respiratory distress. His vital signs were arterial blood pressure, 117/59 mm Hg; heart rate, 133 beats/min; respiratory rate, 36 breaths/min; temperature, 37.4°C; and oxygen saturation, 90% (O_2 at 5 L/min by face mask). He weighed 5.7 kg (10th–25th percentile for age). In the emergency room he required a jaw thrust maneuver to maintain a patent airway. Physical examination demonstrated upper airway rhonchi, intermittent inspiratory stridor, and sinus tachycardia without significant murmur. Initial white blood cell count was 6000/mm^3 with 50% lymphocytes and 46% bands. A lateral neck roentgenogram showed supraglottic edema and an increase in the size of the epiglottis with narrowing of the airway.

A decision was made to transport him to the operating room by physicians expert in airway management for management of presumed epiglottitis. This was accomplished uneventfully with the patient breathing supplemental oxygen and with electrocardiographic and pulse oximeter monitoring. Anesthesia was induced by slow incremental mask inhalation of halothane in oxygen (up to 3.5% inspired concentration). Direct laryngoscopy demonstrated supraglottitis with bilateral arytenoid edema, mild erythema, and a white exudate. Orotracheal intubation was performed. Blood and airway mucosa cultures were obtained and the infant was transported to the Intensive Care Unit.

He remained lethargic and hypotonic and required mechanical ventilation. Culture material obtained intraoperatively revealed heavy normal upper respiratory flora and gram-negative diplococci. *Hemophilus influenzae* was not grown from the culture material. All other culture material (blood, cerebrospinal fluid, and urine) was negative for pathogenic organisms. The patient remained on mechanical ventilation and ceftriaxone but subsequently developed minimally reactive pupils and became progressively weaker by the fifth hospital day. His limbs became floppy and he had only slight movement in his extremities in reaction to deep painful stimuli. Electrical studies using repetitive nerve stimulation at rates of 20 Hz showed an incremental response of approximately 100%, consistent with botulism (5).

Based on the above clinical features and his response to the nerve stimulation studies, infant botulism was considered. Stool cultures grew *Clostridium botulinum* type B (Maryland State Health Department). Three days after his first airway examination in the operating room he was again examined by direct laryngoscopy and found to have near resolution of the supraglottic and arytenoid edema. Because of weakness, the patient required ventilatory assistance. He regained his strength over several weeks and his trachea was subsequently extubated without difficulty.

Discussion

The clinical presentation and neck radiographic findings in this patient strongly suggested acute epiglot-

Accepted for publication March 11, 1992.

Address correspondence to Dr. Rock, Department of Anesthesiology and Critical Care Medicine, Tower 711, Johns Hopkins Medical Institutions, 600 North Wolfe Street, Baltimore, MD 21205.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

titis. The classic findings of acute epiglottitis, including high fever, irritability, lethargy, and severe sore throat, which progress to dysphagia, dysphonia, dyspnea, and drooling, are usually seen in older children. These children usually assume a characteristic upright posture with forward flexion at the waist, forward chin thrust, slight cervical flexion, and resist attempts to place them supine. These presentations are seldom missed. Other causes of UAO such as supraglottitis, laryngotracheobronchitis, and foreign body must be considered.

Infant epiglottitis (<2 yr old) may be very insidious in its presentation, with only mild fever, and no characteristic positioning or drooling. A prodromal illness may be present of several days' duration. The diagnosis of acute epiglottitis in this population of patients may be delayed until severe airway obstruction has occurred (2). Lateral neck films have been suggested to aid in the diagnosis; however, the dangers associated with delay in securing the airway, moving the patient, and the necessity for accompaniment by a skilled laryngoscopist must be kept in mind (1).

A definitive diagnosis of epiglottitis may be made in infants by direct laryngoscopy, which should be performed in a controlled operating room setting under general anesthesia where capabilities for tracheal intubation, cricothyroidotomy, or tracheostomy are at hand (3). These procedures were carried out in our patient and findings in the operating room of supraglottic swelling, inflammation, and exudate supported a diagnosis of UAO of an infectious nature. Subsequent clinical follow-up and evaluation led to the ultimate diagnosis of infant botulism.

Infant botulism has been described as a cause of respiratory distress (6), which is almost always due to progressive weakness culminating in respiratory failure (6,7). As the diaphragm is relatively resistant to neuromuscular block, of which botulism is a type (8), usually the disease is recognized before respiratory failure develops. Our patient was unique, however, in that he had UAO that was associated with supraglottic inflammation and arytenoid edema.

It is important to note that in the approximately 600 cases of infant botulism reported in the literature, periglottic inflammation has not been reported (9,10). While the issue of whether the botulism caused the glottic inflammation or merely occurred in temporal association with it is important, the association of these two entities must now be kept in mind when managing patients with either of these two diseases. Moreover, this case clearly demonstrates the ability of infant botulism to *mimic* other types of acute UAO.

We can only speculate on the possible association of supraglottic swelling and inflammation with botulism. Weakness may result in either (a) supraglottic pooling of secretions with secondary irritation and/or superinfection or (b) collapse of supraglottic structures on inspiration and subsequent swelling and inflammation. This case supports the importance of systematic management of acute UAO (1) and suggests that the differential diagnosis of a hypotonic infant with respiratory distress, drooling, and feeding difficulties should now include botulism.

Clostridium botulinum produces a potent neurotoxin that causes progressive muscle paralysis. *Clostridium botulinum* spores can survive a temperature of 100°C for several hours and moist heat at 120°C for 30 min. The toxin, however, is destroyed by boiling for 10 min. Botulism can occur after ingestion of preformed toxin or after ingestion of *C. botulinum* spores that germinate, proliferate, and then generate toxin in the gastrointestinal tract.

Botulinal toxin affects cholinergic synapses peripherally by interfering with presynaptic release of acetylcholine from preganglionic and neuromuscular junction nerve endings. Weakness appears symmetrically and progresses from facial muscles to the distal extremities. Patients present with blurred vision, dysphonia, dysphagia, and dysarthria. Subsequent symmetric paralysis of the extremities progresses rapidly to involve the diaphragm. Impaired cholinergic autonomic transmission results in constipation, urinary retention, and nausea and vomiting. In an infant, signs and symptoms include poor feeding and failure to thrive, followed by progressive weakness and impaired respirations (6).

On examination, patients are alert and afebrile, with ptosis and failure of accommodation. Pupils are normal in size and react sluggishly. There is weakness of the tongue, larynx, and respiratory muscles. Pooling of oral secretions occurs and may explain the supraglottitis found in this child. Reflexes are diminished or absent but are not pathologic and the sensory examination is usually normal.

Infant botulism is a relatively "new" disease first described in 1976 (5). Approximately 90% of recognized cases occur in patients younger than 6 mo of age. The intestinal tract is colonized with *C. botulinum*, and toxin is gradually produced leading to slower onset of weakness than when preformed toxin is ingested. The diagnosis of infant botulism requires confirmation of botulinal toxin in stool or isolation of *C. botulinum* from stool culture as was found in our patient. Treatment involves aggressive supportive care. Deaths are uncommon and occur principally in rapidly progressive disease before supportive treatments can be instituted. Infants with mild hypotonia, poor feeding, and failure to thrive have been found to have botulism, and there is evidence that 5% of cases

ANESTH ANALG
1992;75:136–8

of sudden infant death syndrome may actually be severe cases of infant botulism (7).

The increased duration of nondepolarizing muscle relaxants associated with the synaptic blockade must be kept in mind. Depolarizing muscle relaxants should be used with caution because of potential denervation hypersensitivity of postsynaptic receptors and the risk of hyperkalemia. Patients presenting to the operating room may also have a "full" stomach, and appropriate precautions should be taken to prevent aspiration. The most important anesthetic considerations relate to airway management. Some very weak patients with botulism will need tracheal intubation to protect the airway and to allow mechanical ventilation. Moreover, this case report illustrates that patients with botulism are at risk for airway obstruction.

Many questions remain unanswered regarding the relatively new disease of infant botulism; nevertheless, we recommend that it should be considered in the differential diagnosis of the hypotonic infant with airway obstruction. In the rush to evaluate the obstructed airway, significant weakness may be overlooked. Hypotonia in an infant with airway obstruction should immediately prompt investigation for botulism.

References

1. Davis HW, Gartner JC, Galvis AG, Michaels RH, Mestad PH. Acute UAO: croup and epiglottitis. Pediatric Clin North Am 1981;28:859–80.
2. Blackstock D, Adderley RJ, Steward DJ. Epiglottitis in young infants. Anesthesiology 1987;67:97–100.
3. Diaz JH. Croup and epiglottitis in children: the anesthesiologist as diagnostician. Anesth Analg 1985;64:621–33.
4. Weibley RE, Holbrook PR. Proximal airway failure in children. In: Shoemaker WC, Ayres S, Grenvik A, Holbrook PR, Thompson WL, eds. Textbook of critical care. Philadelphia: WB Saunders, 1989:241–7.
5. Pickett J, Berg B, Chaplin E, Brunstetter-Shafer M. Syndrome of botulism in infancy: clinical and electrophysiologic study. N Engl J Med 1976;14:770–2.
6. Smith GE, Hinde F, Westmoreland D, Berry PR, Gilbert RJ. Infantile botulism. Arch Dis Child 1989;64:871–2.
7. Long SS. Botulism in infancy. Ped Infect Dis 1984;3:266–71.
8. L'Hommedieu C, Polin RA. Progression of clinical signs in severe infant botulism. Clin Ped 1981;20:90–5.
9. Spika JS, Shaffer N, Hargrett-Bean N, Collin S, MacDonald KL, Blake PA. Risk factors for infant botulism in the United States. Am J Dis Child 1989;143:828–32.
10. Thompson JA, Glasgow LA, Warpinski JR, Olson C. Infant botulism: clinical spectrum and epidemiology. Pediatrics 1980; 66:936–42.

Job's Syndrome: An Unusual Response to a Common Drug

Louis M. Guzzi, MD, and John M. Stamatos, MD

Anesthesia and Operative Services, Walter Reed Army Medical Center, Washington, D.C.

Job's syndrome, or the hyperimmunoglobulin E syndrome, is a rare disorder that was originally described in 1966 (1) and is characterized by recurrent bacterial infections of the skin and the sinopulmonary tract, immunoglobulin E serum levels at least 10 times normal, and neutrophils having a variable chemotactic defect. Most of the infections are secondary to *Staphylococcus aureus*. There is a relative paucity in the literature of described anesthesia-related complications associated with Job's syndrome, even though patients with this syndrome present frequently for abscess drainage. We report a case that describes an atypical response to succinylcholine in a patient with Job's syndrome.

Case Report

A 31-yr-old, 95-kg woman presented with acute cholecystitis and was scheduled for a cholecystectomy. Her past medical history revealed no history of neuromuscular disease or steroid-induced muscle weakness. She had no proximal or distal muscle weakness, lower extremity sensory loss, or other related problems. Several operations had been performed without anesthesia-related complications, both under general endotracheal anesthesia and monitored anesthesia care. These procedures were for recurrent abscesses that required incision and drainage and for orthopedic surgery.

Physical examination on presentation to the operating room revealed an obese woman in mild distress, with multiple skin lesions consistent with Job's syndrome. The patient's laboratory studies included a complete blood count, electrolyte balance, and a liver function panel and were within normal limits, except for a plasma potassium level of 3.5 mEq/L. Preoperative medication included oral prednisone (20 mg every other day), ditropan (5 mg twice a day), omeperazole (40 mg every day), multivitamins, folate, prednisolone eye drops, subcutaneous heparin (5000 U twice a day), and 48 h of intravenous ceftriaxone and tetracycline.

In the operating room, routine monitors were placed, including a peripheral nerve stimulator over the ulnar nerve at the elbow. As the patient breathed 100% oxygen, 3 mg of *d*-tubocurarine, 200 μg of fentanyl, and 1 mg of midazolam were administered intravenously. While cricoid pressure was maintained, thiopental (350 mg) and succinylcholine (120 mg) were administered intravenously. The initial train-of-four twitches diminished to zero of four in approximately 45 s, and the trachea was easily intubated. Controlled ventilation was begun, and isoflurane was used for maintenance of anesthesia. Intermittent use of the peripheral nerve stimulator revealed a gradual increase in the twitch response without fade. Approximately 40 min passed before the baseline train-of-four response returned, as determined by the neuromuscular blockade monitor.

The patient was returned to the operating room 2 wk after this incident for repair of a dehiscence of her cholecystectomy wound. During this operation, the patient did not receive *d*-tubocurarine but was given 1.0 mg/kg of succinylcholine intravenously. Approximately 45 min passed before the train-of-four response returned to baseline.

Postoperatively, the patient's plasma cholinesterase activity was 3.6 IU/mL (4–8 nL), red blood cell cholinesterase was 4998 U/L (3590–6660 nL), and acetylcholine antibody count was negative. The patient also had a normal dibucaine inhibition of 90.5% and a normal fluoride inhibition of 97.5%. Creatine kinase was also noted to be normal.

The records of the patient's two previous operations were obtained, and on both occasions it was noted that the patient demonstrated a prolonged blockade after succinylcholine administration at an appropriate dose.

Discussion

Job's or hyperimmunoglobulin E syndrome is a relatively rare entity, of which little data and rare case

The views of the authors do not purport to reflect the opinions of the Department of Defense (paragraph 4-3, article 360).

Accepted for publication March 16, 1992.

Address correspondence to Dr. Guzzi, Anesthesia and Operative Services, Walter Reed Army Medical Center, Washington, DC 20307–5001.

reports exist. In the anesthesia literature, the only discussion was that by Miller and Mann (2) concerning the potential risk of epidural abscess in patients with this syndrome. However, it is likely that anesthesia providers will see more patients with this disease as life expectancy increases as a result of new drug therapies.

This case presentation reveals a patient with a prolonged response to succinylcholine. There appears to be no obvious reason for this prolongation. The patient's temperature was maintained at >36°C during both operations. The patient was being treated with antibiotics for the first operation but had not received any preoperatively for the second operation. She did have a slightly reduced serum potassium concentration before the first operation, but it was normal immediately postoperatively and was normal at the time of the second operation. None of the patient's medications have been implicated in causing prolongation of the action of succinylcholine. Prednisone has been implicated in the past as causing decreased plasma cholinesterase, but in doses in excess of this patient's dosage regimen (3). Neuromuscular disease has been implicated in causing a prolonged response to succinylcholine, but there was no evidence of myasthenia gravis or the myasthenic syndromes in this patient.

The most common reason for a prolonged neuromuscular blockade from succinylcholine is either decreased plasma cholinesterase or decreased pseudocholinesterase. Plasma cholinesterase is synthesized in the liver, and cirrhosis (4), pregnancy (5), echothiophate usage (5), cytotoxic drugs (6), cancer (7), and angiotensin-converting enzyme inhibitors (8) can all decrease plasma cholinesterase activity and slightly prolong response to succinylcholine. However, Foldes et al. (4) demonstrated that even with decreased levels of pseudocholinesterase to 20% of normal in patients with liver disease, the duration of apnea after succinylcholine administration only increased from 3 to 9 min.

Another common cause of prolonged neuromuscular block is abnormal or variant plasma cholinesterase, as described previously by Kalow and Genest (9). These patients will also have an abnormal dibucaine number. It is important to remember that there may be a normal pseudocholinesterase level and a low dibucaine number, reflecting an atypical enzyme prevalence. Our patient demonstrated none of these disease states. She had a normal dibucaine number and a normal pseudocholinesterase level. There was no other obvious reason for her prolonged response to succinylcholine.

Job's syndrome is a rare and unusual clinical entity, with most problems related to infection and recurrent abscess formation. This atypical response to succinylcholine in a patient with Job's syndrome may be an isolated incident or a clinically significant occurrence related to the underlying disease process.

References

1. Davis SD, Schuller J, Wedgewood RJ. Job's syndrome. Recurrent "cold" staphylococcal abscesses. Lancet 1966;1:1013–5.
2. Miller FL, Mann DL. Anesthetic management of a pregnant patient with the hyperimmunoglobulin E (Job's) syndrome. Anesth Analg 1990;70:454–6.
3. Foldes FF, Arai T, Gentsch HH, Zarday Z. The influence of glucocorticosteroids on plasma cholinesterase. Proc Soc Exp Biol Med 1974;146:918–20.
4. Foldes FF, Randall-Baker L, Birch JH. Causes and prevention of prolonged apnea with succinylcholine. Anesh Analg 1956;35: 609–33.
5. Pantuck EJ, Pantuck CB. Cholinesterases and anticholinesterases. In: Katz RL, ed. Muscle relaxants. Amsterdam: Excerpta Medica, 1975.
6. Miller RD, Savarese JJ. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1990:389–435.
7. Kaniaris P, Fassoulaki A, Liarmukopoulou K, Dermitzakis E. Serum cholinesterase levels in patients with cancer. Anesth Analg 1979;58:82–4.
8. Bentz EW, Stoelting RK. Prolonged response to succinylcholine following pancuronium reversal with pyridostigmine. Anesthesiology 1976;44:258–60.
9. Kalow W, Genest K. A method for the detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. Can J Biochem 1957;35:339–46.

Letters to the Editor

Is Epidural Anesthesia *Really* Better for Major Vascular Surgery?

To the Editor:

Tuman et al. (1) have stated that "epidural anesthesia and analgesia is associated with beneficial effects on coagulation status and postoperative outcome compared with intermittent on-demand opioid analgesia." Their study compared both laboratory and clinical indicators of a hypercoagulable state after either general anesthesia and on-demand parenteral and/or oral narcotic administration or general plus epidural anesthesia followed by epidural opiate and local anesthetic administration. They suggest that the epidural group had a better outcome due to a decrease in stress (presumably secondary to better pain control) in that group compared with the general anesthesia group. They imply that medications administered epidurally have a more beneficial effect than similar medications given by simpler routes. However, their data do not support this conclusion.

As they provide neither objective data about the degree of comfort in the two groups of patients nor details of the pain management provided for patients in the general anesthesia group, it is possible that these patients received opiates by intramuscular injection too infrequently or in too small doses—all common problems with typical postoperative pain management. Patients in the epidural group had a member of a postoperative pain management team supervise administration of the epidural medications. Furthermore, patients in the epidural group probably had a significant degree of sympathetic blockade due to the bupivacaine infusion. Patients in the general anesthesia group apparently did not receive a similar sympathetic block (via oral or parenteral medication).

It seems then that the observed beneficial result may be due to good pain control and sympathetic blockade, rather than due to the route of administration of the medications. Although epidural opiates are frequently used to manage postoperative pain, there is no controlled study comparing this method with other *adequate* means of pain control that indicates that epidural administration has any advantages over effective pain control achieved by other means. In fact, in one controlled study comparing epidural and intravenous fentanyl after cesarean section (2), the techniques were not distinguishable.

Benjamin H. Gorsky, MD
1629 Wilder Avenue #1003
Honolulu, HI 96822

References

1. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991;73:696–704.
2. Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology 1990;72:981–6.

In Response:

Dr. Gorsky raises questions regarding the interpretation of the findings of our recent study (1). He correctly notes that we demonstrated better outcomes after major vascular surgery in patients managed with epidural anesthesia and analgesia (EAA) compared with a similar cohort of patients managed with "routine" on-demand narcotic administration postoperatively. We strongly disagree with Gorsky when he states that our data do not support the conclusion that medications administered epidurally have a more beneficial effect than similar medications given by simpler routes. Our study demonstrates statistically and clinically important differences between the two treatment groups in the rates of cardiovascular, infectious, and overall postoperative complications. Our data present good evidence of a clear association between attenuation of hypercoagulability, a lower incidence of thrombotic events (peripheral arterial graft, coronary artery or deep vein thromboses), and the use of EAA. We believe our methodology and outcome data speak for themselves: when administered to high-risk vascular surgical patients in the manner described, epidural anesthesia and analgesia is superior to routine on-demand narcotic analgesia administered after isoflurane/fentanyl/N_2O anesthesia. The implication that any medication given epidurally will be more beneficial than a similar medication given by a simpler route would be a misinterpretation and overextrapolation of our conclusions. Our findings apply to a specified subset of patients undergoing particular operative procedures and receiving anesthetic and analgesic management according to defined protocols.

Careful examination of our manuscript reveals that we indeed acknowledge that differences in degree of pain control may in part be associated with secondary effects that result in important coagulation and clinical outcome findings. As noted in the discussion of our manuscript, our ". . . study design does not allow confirmation or rebuttal of the hypothesis that improved outcome in the setting described may have been related primarily to different degrees of postoperative analgesia." Because our study was designed as an observational critique of the clinical outcome of two randomly assigned methods of perioperative anesthetic management, interpretation of the findings is limited because specific mechanisms were not sought to explain the intergroup differences.

We disagree with Gorsky's claim that ". . . there is no controlled study comparing . . . [epidural opiates] . . . with other *adequate* means of pain control that indicates that epidural administration has any advantages over effective pain control achieved by other means." Salomaki et al. (2)

©1992 by the International Anesthesia Research Society

demonstrated a clinical advantage of the epidural infusion over the intravenous infusion of fentanyl for analgesia after thoracotomy in a study where each therapy was titrated to achieve similar median pain scores. Soon to be published data from the Perioperative Ischemia Randomized Anesthesia Trial (PIRAT) being conducted at The Johns Hopkins Hospital will independently confirm our findings of decreased hypercoagulability and arterial graft failure (including reoperation) even when epidural anesthesia is used for only 24 h postoperatively compared with intravenous patient-controlled analgesia (3). Although the mechanisms of these beneficial effects of epidural analgesia compared with other forms of analgesia are not yet known, researchers are accumulating data that indicate that differences in pain control may not be the primary means by which EAA can positively affect outcome.

Finally, we cannot adequately stress the extraordinary care with which clinical outcome studies must be interpreted and applied. An important caveat about the interpretation of such studies is the restraint necessary to avoid generalization of findings that may have restricted application. It is not surprising that healthy patients undergoing simple operative procedures such as cesarean section or knee surgery do not manifest outcome differences between epidural and intravenous opiate infusions large enough to be detected when small numbers of subjects are studied (4,5). In contrast, a common feature of those studies that have demonstrated beneficial effects of EAA is the high-risk nature of the patient population and the greater degree of perioperative surgical stress to which patients are exposed (thoracic or major vascular surgery) (1,2,6).

The questions raised by Gorsky are important and, as outlined above, preliminary answers indicate that in certain high-risk patients EAA has beneficial effects that can occur independent of its superior analgesic potential compared with some other methods. Additional studies are necessary to elucidate the mechanisms of these effects and to determine if the properties of EAA not solely related to analgesia can be achieved via alternative methods. Until such studies are conducted and validated, we believe there are sufficient data to mandate the efforts required to deliver EAA to certain high-risk surgical patients.

Kenneth J. Tuman, MD
Robert J. McCarthy, PharmD
Anthony D. Ivankovich, MD
Department of Anesthesiology
Rush-Presbyterian-St. Luke's Medical Center
Chicago, IL 60612

References

1. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Anag 1991;73:696–704.
2. Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural vs intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 1991;75:790–5.
3. Christopherson R, Frank SM, Norris EJ, et al. Reoperation after lower extremity vascular surgery is more common after general than epidural anesthesia. In: Proceedings of the Society of Cardiovascular Anesthesia Meeting, Boston, 1992.
4. Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology 1990;72:981–6.
5. Loper KA, Ready LB, Downey M, et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990;70:72–5.
6. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729–36.

Mass Spectrometers and Infrared Gas Analyzers Interpret Bronchodilator Propellants as Anesthetic Gases

To the Editor:

Infrared gas analyzers and mass spectrometer systems are routinely used in operating rooms for monitoring respiratory and anesthetic gases. Recently, Karasch and Sivarajan (1) reported that mass spectrometer systems, but not infrared anesthetic monitors, may report falsely high readings of isoflurane when halogenated propellants from metered dose bronchodilators are introduced into the anesthesia circuit. We recently noticed that mass spectrometers may also falsely indicate the presence of halothane and enflurane, and that some infrared sensors do indeed detect halogenated propellants as anesthetic gases. This problem came to our attention when Alupent (metaproterenol, Boehringer Ingleheim) was administered to a patient receiving approximately 1% halothane. The Medspect II mass spectrometer suddenly indicated 4% inspired halothane when Alupent was administered via a fitting adjacent to the mass spectrometer port on the anesthetic system "Y" connector. As few as four puffs was able to produce these artifacts. Occasionally, we noticed artifactual enflurane readings. We also found that a Datex Capnomac anesthetic gas analyzer (infrared detector) read approximately 1% halothane when a similar maneuver was performed in the absence of any anesthetic gases. Alupent contains dichlorodifluoromethane, dichlorotetrafluoroethane, and trichlorofluoromethane propellants, as does Atrovent (ipratoprium bromide, Boehringer Ingleheim), and Brethaire (terbutaline, Geigy) metered dose inhalers. Dichlorodifluoromethane and trichlorofluoromethane are propellants in the Proventil brand of albuterol (Schering Corp.), the Ventolin brand of albuterol (Allen and Hanburys), and the Maxair brand of pirbuterol (3M Pharmaceuticals). Proventil produced readings of about 2% isoflurane and 2% halothane when tested with a mass spectrometer, and 0.7%–0.8% halothane when tested with a Datex Capnomac.

Mass spectrometers identify anesthetic gases with the use of discrete fixed collectors located at positions to capture ionized gases of various mass to charge (m/z) ratios. Halothane is detected by an ion of m/z 117; trichlorofluoromethane produces an ion of identical m/z. Both isoflurane and dichlorodifluoromethane and dichlorotetrafluoroethane produce an ion of m/z 87 (1). With the Capnomac infrared detector, halogenated hydrocarbon propellants may be mistaken for halothane because of the relatively high gain used by the analyzer for halothane and the overlap of the infrared spectrum for these compounds.

We were unable to simulate the presence of isoflurane or enflurane with these propellants.

When using bronchodilators with halogenated propellants, clinicians should be aware of the possibility that either mass spectrometer or infrared detection systems may interpret the propellants as anesthetic vapors.

Philip E. Bickler, MD, PhD
Yung J. Sohn, MD
Department of Anesthesia
University of California
San Francisco, CA 94143-0648

Reference

1. Kharasch ED, Sivarajan M. Aerosol propellant interference with clinical mass spectrometers. J Clin Monit 1991;7:172–4.

Masseter Muscle Spasm and the Diagnosis of Malignant Hyperthermia Susceptibility

To the Editor:

Van der Spek (1) and Patel et al. (2), in correspondence on the subject of masseter muscle spasm (MMS) in children following the paper by the latter group (3), express serious doubts as to the validity of in vitro contracture tests (IVCTs) for the diagnosis of malignant hyperthermia (MH) susceptibility. Van der Spek's argument is, however, based on the extrapolation of results between dissimilar groups of patients. Our group has shown (4) that 51% of children *referred* with a history of MMS were classified as susceptible to MH following IVCTs. We cannot stress strongly enough that those patients tested were not the total population of children with MMS, but only those of the estimated 5 million anesthetized where the attending anesthetist considered the MMS of sufficient severity to raise the possibility of MH. As was stated in our paper (4), some of our patients had generalized rigidity: the exact number is unclear as this sign was not always looked for or reported. We assume that other papers reporting a similar incidence of positive IVCT following MMS (5,6) were subject to similar patient selection processes. It is therefore naive of van der Spek (1) to suggest that 50% of Littleford's patients (3) may be labeled susceptible to MH. It is most likely, in fact, that those in Littleford's "isolated" MMS group would not have been considered for biopsy in our center as it is apparent that the attending anesthetists did not consider the response abnormal and hence their decision to carry on with triggering drugs (cf generalized rigidity group). However, we would have to reserve final judgment without access to all relevant information on individual cases.

The reservations about IVCT expressed by Patel et al. (2) are strictly correct: that is, we do not know for sure whether a positive IVCT result always indicates true MH susceptibility. Indeed, when the European MH group diagnostic criteria were formulated (7), threshold contracture values were assigned to err on the side of caution. Thus, most diagnostic centers accept that some false-positive diagnoses are made. On the basis of testing control muscle according to the European MH group protocol, the false-positive rate is estimated to be of the order of 4% (8), a figure far short of the 50% implied by van der Spek (1). Until there is a 100% sensitive and specific genetic test for MH, the true false-positive rate for the IVCT will not be known because, given the availability of alternative safe anesthetic drugs, patients with positive IVCT results should not receive triggering agents.

The fact that patients do not develop hypermetabolism when given triggering anesthetic drugs does not mean that they are not susceptible to MH. In our series, MH susceptible patients have had, on average, three uneventful anesthetics before their reaction or prior to a positive family history emerging (9). One patient had 13 apparently normal anesthetics, whereas her similarly susceptible brother died on first exposure. The cause of this phenomenon remains as one of the challenges of MH research, but its occurrence is of great clinical importance, both to individual patients and their blood relatives. It would surely be an indefensible tragedy if patients were assumed not to be susceptible to MH because they did not develop fulminant MH after abnormally severe MMS, only for them or a relative to die from MH at a later date.

Therefore, we must emphasize that any patient with *abnormally severe* MMS must be considered MH susceptible until proven otherwise. At present, the only method for establishing nonsusceptibility to MH is to demonstrate a normal IVCT response. Any other course of action, as stated by Rosenberg and Shutack (10) is courting risk, and with the availability of safe nontriggering anesthetic drugs must be considered irresponsible.

F. R. Ellis, PhD, FRCAnaes
P. M. Hopkins, MB, BS, FRCAnaes
P. J. Halsall, MB, ChB
A. S. Christian, MB, ChB, FRCAnaes
Department of Anaesthesia
St. James's University Hospital
Beckett Street
Leeds LS9 7TF
United Kingdom

References

1. Van der Spek AFL. Triggering agents continued after masseter spasm: there is proof in this pudding! Anesth Analg 1991;73:364–5.
2. Patel LR, Bose D, Littleford JA. Masseter muscle spasm in children. Anesth Analg 1991;73:362–3.
3. Littleford JA, Patel LR, Bose D, Cameron CB, McKillop C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. Anesth Analg 1991;72:151–60.
4. Christian AS, Ellis FR, Halsall PJ. Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? Br J Anaesth 1989;62:540–4.
5. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161–4.
6. Flewellen EH, Nelson TE. Halothane-succinylcholine induced masseter spasm: indicative of malignant hyperthermia susceptibility? Anesth Analg 1984;63:693–7.
7. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anaesth 1984;56:1267–9.
8. Ording H, for the European MH Group. Experience with the European protocol for contracture testing. J Neurol Sci 1990;98S:522.
9. Ellis FR, Halsall PJ, Harriman DGF. The work of the Leeds Malignant Hyperpyrexia Unit 1971–1984. Anaesthesia 1986;41:809–15.
10. Rosenberg H, Shutack JG. Masseter muscle spasm in children. Anesth Analg 1991;73:361–2.

ANESTH ANALG
1992;75:141–56

In Response:

Dr. Ellis et al. "cannot stress strongly enough that [only] those [MMS patients were tested in which] . . . the attending anesthetist considered the MMS of sufficient severity to raise the possibility of MH" and in which the attending anesthetist had *referred* the patient to a testing center. And further: "We must emphasize that any patient with *abnormally severe* MMS must be considered MH susceptible until proven otherwise." These opinions emphasize selection bias with respect to testing of MMS patients, which may be an important weakness rather than a virtue.

Thus, Dr. Ellis et al. concede that not all patients with MMS were referred to, or were considered severe enough to need to be referred to, their center. Then what percentage of instances of MMS is actually severe enough to be referred? Who's to know or judge? Have all these patients been referred because only wise, experienced "attending anesthetists" referred these patients to their center? Or are there perhaps anesthesiologists who are less experienced vis-à-vis pediatric practice? Or those who just don't know what to make of this morass? Perhaps, there are "hyper" or scared ones, too? Perhaps, they live in a medicolegal climate where continuation of anesthesia is professional suicide? Perhaps, the family is particularly insistent on referral? All of these and many more uncertainties contribute to the selection criteria leading to the ultimate decision to go ahead with referral and biopsy. Do Dr. Ellis et al. "see" 1% (or 5% or 10%) of patients with MMS? Does that mean that 99% of patients with "MMS" have no "problems" whatsoever? And, parenthetically, can we continue anesthesia, as before, especially now that we have specific monitoring for hypermetabolism (end-tidal CO_2)? Or are there other signs that may help us differentiate the MMS patients without problems from those with rare symptoms—eg, limb and trunk rigidity? The latter is a suggestion made by Dr. Patel's group—experienced attending pediatric anesthesiologists—who established their practice of continuation of triggering anesthesia well before the current plethora of articles with contrary advice (1). Has the average prudent anesthesiologist already recognized this, and is that the reason why Dr. Ellis is only referred a small percentage of the MMS population? Concluding that masseter spasm must have been "clinically significant" *because* patients were referred is a fallible premise. If Dr. Ellis' test is only applicable to patients who have been selected and referred by the proverbial attending anesthetist, and not to *all* subjects who presented with masseter spasm, the IVCT's usefulness is in doubt (2,3). The attending anesthetist cannot be the gold standard, nor set the threshold, for masseter spasm—such an anesthetist does not exist. If a test, developed and applied to a poorly defined, selected sample of the MMS population, cannot be generalized to the population with MMS, then one cannot make inferences on the basis of the outcome of that test in the MMS population (3).

To make matters worse, when definitions of masseter spasm and MH are vague and arbitrary, retrospective data collection (as in Dr. Ellis' [4, 5] and others' studies) compounds bias. Once suspicion of MH has been stirred, a "charged" environment has been created in which it can be hard to take a cold look at the facts: one wants (or even needs) a "positive" diagnosis, and memory becomes unusually selective.

Thus, we are provided with classic examples of selection, interviewer, and recall bias (6). The epidemiology literature is fraught with examples of associations and causality, only to be shown to have been "discovered" erroneously—on the basis of bias.

I did not mean to imply a false-positive rate of the IVCT of 50%, far from it. I wondered whether we know, *at all*, what the tests mean, whether they be positive or negative. If none of the *isolated* masseter spasm patients of the Winnipeg group developed MH (and they didn't in my opinion, nor in the opinion of experienced attending pediatric anesthesiologists [1]), one wonders why a number of MH testing centers seem to converge on 50% positivity of the IVCT in MMS patients. These MH centers are unlikely to all have the very same selection criteria (and biases). As the devil's advocate, I can argue that the tests followed a "theorem of probability": the predictable odds of a coin flip, 50% tails (positive) and 50% heads (negative), provided one performs the tests often enough. . . . Thus, the IVCT's outcome can support the assertion that the association of a positive IVCT with the occurrence of MMS, is *not unlikely* to be one of chance (6). The reason different positive rates are observed among centers is also explainable (if not predictable) on the basis of sample size, test techniques, selection and observation bias, and confounders—to name a few. Even *if* we were to assume a 100% sensitivity of the European IVCT, a specificity of 96% (7), and an MH prevalence of 1 in 10,000, the predictive value of a positive IVCT would be 0.2% and, thus, we would label subjects with a positive IVCT MH susceptible 99.8% of the time, *even though they are MH negative!* (2,8). Assuming a specificity of 85% as recently proposed by the North American Malignant Hyperthermia Registry (9), the predictive value of a positive test is only 0.06%.

Even *if* an association of a positive IVCT and MMS has been established *not* to be likely due to chance, bias, or confounding, one has to ask: "What does that have to do with the price of eggs," or MH, in this case (6). So far it was assumed, for the purposes of this argument, that a clear definition of MH existed, because without one, a test's sensitivity or specificity cannot be identified—let alone its false-positive rate be established. Case reports and series of MMS are useful for raising the question of the presence of an association with MH, but they are not useful for testing hypotheses (6). Furthermore, each case should be scrutinized to ascertain if it conforms to the definitions of the disease and whether possible confounders (eg, a myotonia, muscular dystrophy, or lack of ventilation or oxygenation) are present. From a review of presumed MH cases at the last North American MH Registry meeting (10), from those incidentally discussed at the Fifth International MH workshop (11), and from the case literature, it has become apparent that a consensus on a definition of disease (MH) has not been achieved. Thus, sensitivity and specificity data of a test proposed to identify MH should be presented with the determinants of disease in each case since its definition varies. If these data are not presented, one cannot assess what was accepted as a true case of MH and,

thus, which test should have been regarded as true positive. Such data have not been presented in the literature by the European MH group (7,12) nor by Dr. Ellis' group (13). In fact, Dr. Ellis et al. concede that a positive IVCT has *not* been *proven* to identify humans who will respond with hypermetabolism (MH) when exposed to trigger agents (vide supra).

The development of a genetic test for MH may not be the panacea to our troubles either, as it is unlikely, if not impossible (2), that a 100% sensitive and specific "genetic" test can be developed to determine whether an individual will manifest MH. The current genetic studies of MH focus on the examination of MH's patterns of inheritance using linkage analyses, ie, how does a determinant of a disease (ie, MH, or usually in its stead a positive IVCT) segregate in a pedigree with the known locations of other DNA markers on the chromosomes. Under favorable conditions, a positive linkage may place a possible mutation within one or two million base pairs from a known maker. Then one or more, of possibly many, mutations in that DNA region need to be identified and shown to be associated with the MH phenotype (again as determined by a positive IVCT) in that pedigree. Another strategy is to *assume* that the MH phenotype is associated with an enzyme or receptor (eg, ryanodine receptor), and follow the segregation of the MH phenotype in the pedigree with that of the markers for the enzyme or receptor under suspicion. Then, mutation(s) of these enzymes or receptors are identified and their segregation is compared to pedigrees with an MH phenotype. In either case, a diagnostic DNA probe(s) needs to be developed. The point is that in all approaches reliable determination of the MH phenotype (eg, by a test like the IVCT) is a sine qua non. Furthermore, even if one or more specific DNA probes have been developed, they will not be able to identify other, or not yet discovered, or new mutations that may also be responsible for one or more MH phenotypes (eg, genetic heterogeneity). Even when an MH mutation has been identified in an individual, it does not mean that the disease will manifest itself. Phenotype depends on many factors including heterozygosity, penetrance, and expression. In addition, coexisting genotypes, phenotypes, and other circumstances (presence or absence of hormones, enzymes, or environmental factors) may be needed for, or may prevent, manifestation of MH in an individual (eg, multifactorial and epistatic inheritance) (14).

I agree that we should be prudent and act in the best interest of our patients; however, unless we are forthright about the limitations of our research and exercise sound judgment in the conduct of our research as well, we may do our patients and the field of anesthesiology a disservice, if not harm, by coming to diagnoses, therapies, and resulting socioeconomic conditions without proper foundations.

Abraham van der Spek
Department of Anesthesiology, Pediatrics
C. S. Mott Children's Hospital
Room C 4139, Box 0800
Ann Arbor, MI 48109-0800

References

1. Littleford JA, Patel LR, Bose D, Cameron CB, McKillop C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. Anesth Analg 1991;72:151–60.
2. Galen RS, Gambino SR. Beyond normality: the predictive value and efficiency of medical diagnoses. New York: John Wiley & Sons, 1975.
3. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Diagnosis. In: Clinical epidemiology. A basic science for clinical medicine. 2nd ed. Boston: Little Brown, 1991:1–153.
4. Ellis FR, Halsall PJ. Suxamethonium spasm: a differential diagnostic conundrum. Br J Anaesth 1984;56:161–4.
5. Christian AS, Ellis FR, Halsall PJ. Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? Br J Anaesth 1989;62:540–4.
6. Hennekens CH, Buring JE. Basic concepts. In: Epidemiology in medicine. Mayrent SL, ed. Boston: Little Brown, 1987:3–93.
7. Ording H, for the European MH Group. Experience with the European protocol for contracture testing. J Neurol Sci 1990;98S:522.
8. Winkel P, Statland B. Interpreting laboratory results: reference values and decision making. In: Clinical diagnosis and management by laboratory methods. Henry JB, ed. Philadelphia: WB Saunders, 1991:53–5.
9. Larach MG, Landis JR, Schaeffer-Bunn J, Diaz M, the North American Malignant Hyperthermia Registry. Prediction of malignant hyperthermia susceptibility in low-risk subjects. Anesthesiology 1992;76:16–27.
10. The Fourth MH Biopsy Standards Conference, Pennsylvania State College of Medicine, Hershey, Pa., November 22–24, 1991.
11. Fifth International MH Workshop, Universität München, Klinikum Rects der Isar, München, Germany, September 21–23, 1990.
12. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anesth 1984;56:1267–9.
13. Ellis FR, Halsall PJ, Harriman DGF. The work of the Leeds Malignant Hyperpyrexia Unit 1971–1984. Anaesthetist 1986;41:809–15.
14. Gelehrter TD, Collins FS. Principles of medical genetics. Baltimore: Williams & Wilkins, 1990.

In Response:

Although patients exhibiting fulminant MH usually test positive on the halothane/caffeine contracture test, there are few data on whether screened subjects testing positive also exhibit a positive clinical episode (1). The likelihood of getting false-positive results with any screening test depends on the criteria for selecting cases for biopsy testing. Thus if the patients to be tested are well selected (ie, restricted by very strict criteria of clinically detectable hypermetabolism associated with generalized muscular rigidity and typical febrile episode), then there are fewer false-positive results. Whether one is justified in considering isolated MMS as MH can be argued, but it seems plausible based on previous biopsy data (2,3). Further studies on the series of patients reported in our study (1) by halothane/caffeine contracture testing (unpublished data) suggest that in 9 of 27 patients with transient MMS tested so far, who did not experience fulminant MH despite continuation of triggering anesthetics, a positive biopsy result based on North American Malignant Hyperthermia biopsy testing criteria was seen. Dr. Ellis and colleagues, probably based on the transient rigidity experienced in our series of patients, may not have chosen to perform a biopsy on many of them. However, would they follow the same course of action if they had known that even these patients have a fairly significant incidence of positive muscle biopsy results? Because the same individual, afflicted with the genetic hypermetabolic disorder that is triggered by anesthetic agents, can present at different times with pictures of different clinical severity, a cautious approach by many anesthetists is justifiable. Our data simply indicate that muscle biopsy results cannot be uncritically accepted. Meanwhile, complete reliance on nontriggering agents may be the answer for some. For others opting to continue with the triggering anesthetic agents, there is no substitute for

ANESTH ANALG
1992;75:141–56

extreme vigilance in monitoring and familiarity with resources for dealing with a crisis. Data obtained from the latter type of experience will be invaluable for laboratories and organizations that are trying to validate the performance and interpretation of contracture tests in muscle biopsy specimens.

Deepak Bose, MD, PhD
Department of Pharmacology and Therapeutics, Anesthesia and Internal Medicine
62 Emily Street
Winnipeg, MB
Canada, R3E OW3

References

1. Littleford JA, Patel LR, Bose D, Cameron CB, McKillop C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. Anesth Analg 1991;72:151–60.
2. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161–4.
3. Christian AS, Ellis FR, Halsall PJ. Is there a relationship between masseteric muscle spasm and malignant hyperpyrexia? Br J Anaesth 1989;62:540–4.

Isolated Masseter Muscle Spasm Versus Generalized Rigidity?

To the Editor:

Much controversy still exists regarding the management of patients who have isolated "masseter muscle spasm (MMS)" following halothane and succinylcholine administration. There is less controversy regarding generalized rigidity in combination with MMS. Generalized muscle rigidity has been shown to be a predictor of malignant hyperthermia susceptibility (1). In a recent study (2), Littleford et al. surmise that anesthesia can be continued safely in cases of isolated MMS. However, the perioperative management differed considerably in children who demonstrated signs of MMS plus generalized muscle rigidity. The clinical presentations in this latter group were so suggestive of the diagnosis of incipient malignant hyperthermia that anesthesia was stopped in all of these cases and four of the 11 children were given dantrolene. Thus, the author has made a clear distinction between the management of isolated MMS and MMS with generalized rigidity.

We report a case that blurs the distinction between isolated MMS and generalized rigidity and raises questions about appropriate management. A 5-yr-old, 17-kg healthy child without neuromuscular diseases was admitted for adenoidectomy with bilateral myringotomies and tubes. Family history was negative for adverse anesthetic reactions. A halotane inhalation induction of anesthesia was performed without problems. Succinylcholine, 20 mg, was administered intravenously, and endotracheal intubation was attempted after 1 min. The anesthesiology resident could not open the patient's mouth. No other rigidity was noted. In particular, the child was easily ventilated and the extremities did not appear stiff. The arm was lifted to gain access to the intravenous. No rigidity was noted. A second 20-mg dose of succinylcholine was given intravenously. The jaw remained stiff and now the arms and legs appeared tense. The legs could not be bent and the arms were difficult to flex. The anesthetic was aborted. Initial arterial blood gases were pHa 7.22, $Paco_2$ 42 mm Hg, Pao_2 297 mm Hg, base excess −12 mmol/L. The creatinine phosphokinase increased to 2598 IU within 24 h. Myoglobinuria was treated with mannitol. The child made an uneventful recovery.

Experienced anesthesiologists noted *isolated* MMS after the first dose of succinylcholine and *generalized* muscle rigidity after the second! If the first episode of MMS in this patient had not been followed by more succinylcholine, then Littleford et al.'s recommendations would have suggested continuing administration of triggering drugs. The additional dose of succinylcholine placed this patient in the clinical group where Littleford et al. would not continue giving triggering drugs. Is this patient at risk for malignant hyperthermia? Will some patients with malignant hyperthermia susceptibility show isolated MMS to a first dose and generalized rigidity to a second or a larger dose of succinylcholine?

Cases such as the above suggest caution when one is faced with isolated MMS. Until this issue is further resolved we recommend that triggering drugs not be given after isolated MMS.

Richard Kaplan, MD
Matthew Becker, MD
Lynn Broadman, MD
Department of Anesthesiology
Children's National Medical Center
111 Michigan Avenue, NW
Washington, DC 20010

References

1. Larach MG, Rosenberg H, Larach DR, Broennle AM. Prediction of malignant hyperthermia susceptibility by clinical signs. Anesthesiology 1987;66:547–50.
2. Littleford JA, Patel LR, Bose D, Cammeron CB, McKillop C. Masseter muscle spasm in children: implications of continuing the triggering anesthetic. Anesth Analg 1991;72:151–60.

In Response:

Dr. Kaplan et al. describe a presumably rare clinical situation in which their patient received a second dose of succinylcholine after developing isolated MMS subsequent to an initial dose of this drug. The patient then exhibited generalized rigidity. This situation is not comparable to that reported in our case series, where the patients were separated retrospectively into two groups based on their response to a single dose of succinylcholine (i.e., isolated MMS, MMS plus generalized rigidity). None of these patients received a second dose of succinylcholine, and we have never advocated this practice.

There are no published data that describe the clinical sequelae of administering a second dose of succinylcholine after MMS develops. Are the authors implying this practice would unmask the susceptibility to malignant hyperthermia?

Whether the presence of isolated MMS heralds malignant hyperthermia is still debatable and, given the complexity of the processes that trigger the development of malignant hyperthermia, it may always remain an enigma.

Masseter muscle spasm and malignant hyperthermia may represent two extremes of the same disease process. It is possible that even without the second dose of succinylcholine, if the inhaled anesthetics had been continued in their case, this patient may have gone on to develop signs and symptoms of malignant hyperthermia. For this reason, there is no substitute for vigilant clinical and biochemical monitoring.

Leena R. Patel, MD, FRCPC
Department of Anesthesia

Deepak Bose, MD, PhD
Department of Pharmacology and Therapeutics

Judith A. Littleford, BSc, MD
Department of Anesthesia
University of Manitoba
840 Sherbrook Street
Winnipeg, Manitoba R3A 1S1
Canada

Ventilatory Effects of Clonidine

To the Editor:

The study by Benhamou et al. (1) is welcomed given that there is still little information on the respiratory effects of clonidine in humans.

We share the authors' admonition of prescribing clonidine premedication based on their finding of obstructive respiratory disturbances associated with arterial oxygen desaturation in some of their clonidine pretreated subjects. On scrutinizing their table of results, it is interesting that minute ventilation and tidal volume were lower at all time periods after clonidine pretreatment compared with placebo. Statistical significance may be absent because the power of the study was not sufficient to detect the difference. It would have been interesting if the authors also looked at the ventilatory response of these volunteers to carbon dioxide challenge. We have previously reported the attenuation of ventilatory response to carbon dioxide after intravenous administration (3 μg/kg) of clonidine to volunteers (2).

Given the burgeoning interest in clonidine and other more selective α_2-adrenergic agonists in anesthesia, the finding of respiratory effects will be clinically important. It is worth remembering the cautionary note sounded by Dr. Hamilton in his editorial addressing this class of compounds (3). Given the necessity of a functional sympathetic nervous system for survival, he has questioned the rationale of administering such drugs that are sympatholytics. He has suggested more safety studies to assess how the responses to the challenges of blood loss, carbon dioxide excess, hypoxia, and acidosis will be affected.

R. Ooi, FCAnaes
S. A. Feldman, FCAnaes
Magill Department of Anaesthetics
Westminster Hospital
London SW1 2AP
England

References

1. Benhamou D, Veillette Y, Narchi P, Edoffey C. Ventilatory effects of premedication with clonidine. Anesth Analg 1991;73:799–803.
2. Ooi R, Pattison J, Feldman SA. The effects of intravenous clonidine on ventilation. Anesthesia 1991;46:632–3.
3. Hamilton WK. Fashion, Darwin, and anesthetics as poisons. Anesthesiology 1988;69:811–2.

Dr. Benhamou has declined to reply.

An Unusual Cause of Nasogastric Tube Obstruction

To the Editor:

Recently, a 43-yr-old woman traveled to Boston from the Dominican Republic to undergo a mitral valve replacement. The anesthetic management and the surgical procedure were uneventful. On the second postoperative day, after the trachea had been extubated, a nurse reported that the nasogastric tube was obstructed. After some manipulations, it was removed. Examination of the nasogastric tube revealed a large roundworm measuring approximately 30 cm long partially inside its distal end. The specimen was send to Microbiology and it was identified as an adult female *Ascaris lumbricoides* (Figure 1). Although roundworms are relatively rare in northern urban centers, anesthesiologists should be aware of the possibility of this infestation, particularly in patients from endemic areas. These worms can be vomited and aspirated causing asphyxia and death. Obstruction of endotracheal tubes by *Ascaris lumbricoides* has been reported in circumstances related and unrelated to anesthesia and surgery (1,2).

Rafael Ortega, MD
Department of Anesthesiology
Boston University School of Medicine
88 East Newton Street
Boston, MA 02118



Figure 1. Adult female *Ascaris lumbricoides*.

ANESTH ANALG
1992;75:141–56

References

1. Nicholson JP, Kreiger K, Hartman B, et al. Cardiac arrest post operatively in a patient infected with *ascaris*, the roundworm. Chest 1989;96:922–3.
2. Imbeloni LE. Fatal obstruction of an endotracheal tube by an intestinal roundworm. Respir Care 1984;29:368–70.

Relief of Pain by Ketorolac or Alcohol?

To the Editor:

I read the article by Vanos et al. (1) describing the use of ketorolac as an intravenous regional block technique for the treatment of reflex sympathetic dystrophy. This work appears promising; however, the authors are correct in stating that further work needs to be performed before any final conclusions are drawn. For example, what is the effect of the diluent, ethyl alcohol, 10% by weight, in the formulated ketorolac for intramuscular use? If this was the preparation used, I would suggest the authors add an ethyl alcohol solution to their future blinded studies. If ketorolac, indeed, is a successful treatment, its release as a "by mouth" medication would be welcome and useful.

Duke B. Weeks, MD
Department of Anesthesia
The Bowman Gray School of Medicine
300 South Hawthorn Road
Winston-Salem, NC 27103

Reference

1. Vanos DN, Ramamurthy S, Hoffman J. Intravenous regional block using ketorolac: preliminary results in the treatment of reflex sympathetic dystrophy. Anesth Analg 1992;74:139–41.

In Response:

We appreciate Dr. Weeks' comment regarding the ethyl alcohol contained in the ketorolac solution. This is a valid point which deserves further study. However, when the ketorolac was administered by the intravenous regional technique, it was diluted in 40 or 50 mL of solution, resulting in a very dilute concentration of alcohol (0.5%). We believe that the effect is more likely due to the ketorolac itself. Although an oral preparation would certainly be easier to administer, the advantage to the intravenous regional technique is that medications that act peripherally may be given in a concentrated form to the area. If administered orally, extremely high doses would be required to achieve the same concentration in the affected area, such that side effects would prevent its use.

David N. Vanos, MD
Somayaji Ramamurthy, MD
Joan Hoffman, RN
The University of Texas
Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, TX 78284-7838

Effects of Adenosine After Coronary Artery Bypass Surgery

To the Editor:

Recently Zäll et al. (1) reported on the effects of adenosine after coronary artery bypass surgery. In the accompanying editorial, Lillehaug and Tinker (2) followed up with a provocative statement: "If the forerunner of the latter is that of Zall et al., the future of adenosine as a vasodilator does not look good."

However, a similar study previously reported by Torsell et al. (3) had concluded that at low nonhypotensive doses of adenosine, coronary blood flow increased, myocardial perfusion pressure was essentially maintained, and there was no indication of electrocardiographic (ECG) evidence of myocardial ischemia. Thus, perioperative and postoperative low-dose adenosine infusion could be beneficial. This view is also substantiated by Zäll's data at infusion rates of less than 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

The study by Zäll et al. identified six patients as having myocardial ischemia based on the abnormalities of lactate metabolism or ECG changes. However, the study was done shortly after weaning from cardiopulmonary bypass, ie, at a time when patients are still in fluctuating conditions: 9 of 14 (64%) had an abnormal metabolic state before adenosine administration. If adenosine was the cause of metabolic aggravation of the myocardium, then a worsened condition could be expected in these patients. Yet, this did not occur. On the contrary, the metabolic data at "postadenosine 0" showed improvement when compared with control values. Lactate assay of the blood during adenosine infusion may not be a reliable indicator of myocardial ischemia. Infused adenosine is extensively taken up by blood cells, especially the erythrocytes, and it is rapidly metabolized to lactate which in turn diffuses into the bloodstream causing spuriously high lactate levels (4,5). Moreover, the criteria followed by the authors to determine the patients with signs of myocardial ischemia are questionable. For example, in patients 3, 4, 5, and 6, there is no consistent relationship between adenosine dosages and regional myocardial lactate uptake values and ECG changes. (See Table 1, which presents data of patients extracted from Zäll's Tables 3 and 4.) Furthermore, ECG abnormalities are frequently seen in surgery after coronary bypass. High incidence of more severe ECG changes has been reported shortly after coronary bypass (6); and ST segment depression has been considered the least specific index to indicate myocardial ischemia during this phase of coronary artery bypass surgery.

Thus, it is not possible to hold adenosine as the only accountable reason for the metabolic and/or ECG changes observed in the study, as these could have occurred even in the absence of adenosine. Relying upon a single indicator to determine myocardial ischemia seems a precarious criterion, as there is no distinctive feature specific for hyperlactatemia or ECG abnormalities during adenosine infusion after coronary artery bypass surgery. The metabolic and ECG data are confounded and inconsistent. Therefore, we believe that the data provided by Zäll et al. (1) are elusive

Table 1. Effects of Adenosine on Regional Myocardial Lactate Uptake and Electrocardiogram

		Adenosine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	Patient	0	15	30	60	120	0
1	RMLU	6	− 6	− 5	−11	− 11	− 4
	ECG	± 0	± 0	± 0	− 0.05	− 0.1[a]	− 0.05
2	RMLU	6	3	−20[b]	−22[b]	− 29[b]	− 3
	ECG	− 0.15	− 0.15	− 0.2	− 0.25[a]	− 0.25[a]	− 0.15
3	RMLU	4	− 8	− 7	− 2	− 13	− 7
	ECG	± 0	± 0	± 0	− 0.05	− 0.05	± 0
4	RMLU	− 5	−16	− 8	−83[b]	−161[b]	− 3
	ECG			0.1	0.1	0.1	0.1
5	RMLU	−12	−11	−54[b]	−15	− 14	− 8
	ECG	0.15	0.15	0.1			
6	RMLU	−21	−46[b]	−16	−21	− 21	−19
	ECG	± 0	± 0	− 0.05	− 0.15[a]	− 0.15[a]	− 0.05

RMLU, regional myocardial lactate uptake; ECG, electrocardiogram.
Data extracted from Tables 3 and 4 of Reference 1.
Adenosine-induced aggravation of myocardial ischemia:
[a]Further depression of the ST segment of ≥0.1 mV.
[b]Further decrease in RMLU (>20 μmol/min) compared with control.

and do not provide sufficient evidence to support their conclusion that adenosine at low doses may cause myocardial ischemia shortly after coronary artery bypass surgery.

Atsuo F. Fukunaga, MD, PhD
Department of Anesthesiology
Harbor-UCLA Medical Center
1000 West Carson Street
Torrance, CA 90509

Tadaomi Miyamoto, MD
Department of Cardiovascular Surgery
Kokura Memorial Hospital
Kokura, Kitakyushu
Japan

References

1. Zäll S, Milocco I, Ricksten S-E. Effects of adenosine on myocardial blood flow and metabolism after coronary artery bypass surgery. Anesth Analg 1991;73:689–95.
2. Lillehaug SL, Tinker JG. Why do "pure" vasodilators cause coronary steal when anesthetics don't (or seldom do)? Anesth Analg 1991;73:681–2.
3. Torsell L, Ekeström S, Sollevi S. Adenosine-induced increase in graft flow during coronary bypass surgery. Scand J Thorac Cardiovasc Surg 1989; 23:235–9.
4. Lowy BA, Jaffe ER, Vanderhoff GA, et al. The metabolism of purine nucleosides by the human erythrocyte in vitro. J Biol Chem 1958;230:409–19.
5. Paglia DE, Valentine WN, Tartaglia AP, et al. Control of red blood cell adenine nucleotide metabolism studies of adenosine deaminase. In: Brewer GJ, ed. The red cell. New York: Liss, 1978:319–35.
6. Leung JM, Hollenberg M, Mangano DT. Prognostic significance of ST-segment elevation in CABG surgery. Anesthesiology 1991;75(Suppl): A84.

In Response:

We appreciate the interest of Drs. Fukunaga and Miyamoto in our study (1). They claim that lactate assay may not be a reliable method to judge myocardial ischemia during adenosine infusion, as adenosine is taken up and metabolized to lactate by erythrocytes and then diffuses into the blood causing "spuriously high lactate levels." In our study (1), adenosine infusion did not cause any significant changes in arterial blood lactate concentration. Even if arterial lactate levels were increased by adenosine via the erythrocytes, this mechanism cannot explain why in some patients lactate is released from a certain region of the left ventricle, drained by the great cardiac vein, during adenosine infusion.

They also question our criteria used to define myocardial ischemia. Regional myocardial lactate production, one criterion for myocardial ischemia, is a highly sensitive indicator of regional myocardial ischemia (2). Reversible ST-segment depression ≥0.1 mV has been used recently by several investigators (eg, 3,4) to diagnose myocardial ischemia postoperatively after coronary artery bypass surgery. Smith et al. (3) could demonstrate, using the same ECG criteria for myocardial ischemia as we have used, that ischemia is more prevalent postoperatively than preoperatively. Furthermore, they showed that the incidence (26%) of postoperative ischemia peaks shortly (2 h) after revascularization and is related to adverse outcome. We agree with Fukunaga and Miyamoto that "ECG abnormalities are frequently seen in surgery after coronary bypass." This is probably due to the fact that many patients really are ischemic shortly after bypass surgery, as demonstrated by others (3,4) and by us (64% had regional myocardial lactate production before adenosine infusion). Although more severe ECG changes have been reported shortly after coronary bypass by Leung et al. (5), they could not demonstrate that the incidence of reversible ST-segment elevation (16%) was related to an increased incidence of myocardial injury. We do not understand the statement: "ST segment depression has been considered the least specific index to indicate myocardial ischemia during this phase of coronary artery bypass surgery." Compared to what other index? What is the source behind this conclusion?

We agree with Fukunaga and Miyamoto that there was no consistent relationship between metabolic (regional myocardial lactate uptake) and ECG signs of myocardial ischemia. Our data are, however, in agreement with a recent report showing that there is a low concordance

between ECG signs and metabolic (lactate production) signs of regional myocardial ischemia (6). Patients 1, 2, and 3 converted from a net regional myocardial lactate uptake before adenosine infusion to net regional lactate production at low infusion rates of adenosine (15–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Two of these patients (1,2) also developed ECG signs of myocardial ischemia at a nonhypotensive dose of 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In patient 4 it is quite obvious that adenosine to a great extent aggravates myocardial ischemia at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. It is difficult to explain why lactate production in patients 5 and 6 is aggravated at 15 (patient 6) and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (patient 5) but not at higher infusion rates. On the other hand, in patient 6 there is a clearcut and pronounced ST-segment depression at the low, nonhypotensive dose of 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Furthermore, in the whole material there was a significant depression of the ST segment at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$).

Torsell et al. studied the effect of 30–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of adenosine on coronary artery graft flow (7). Possible signs of myocardial ischemia was detected only by ECG in their study. Graft flow increased by 84%, which is in accordance with a 60% increase in great cardiac vein flow in our study at an adenosine infusion rate of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Torsell et al. could not demonstrate ECG signs of myocardial ischemia during low-dose adenosine infusion. Their results are therefore not "substantiated by our data," as we have demonstrated that low-dose adenosine infusion may in some patients cause metabolic and/or ECG signs of regional myocardial ischemia.

The interpretation of Fukunaga and Miyamoto that the "metabolic data at postadenosine 0 showed improvement when compared with control" is not correct. There was no significant difference between pre- and postadenosine control values of regional myocardial uptake. We agree that we chose a difficult time period to study the effects of adenosine on myocardial blood flow and metabolism after coronary artery bypass surgery. We have, however, presented data to confirm that the patients were not in "fluctuating conditions," and this is discussed in detail in the Discussion section of our report (1).

Our data are not "confounded," "inconsistent," or "elusive." Instead we have provided evidence that adenosine may in some patients induce myocardial ischemia, even at low, nonhypotensive infusion rates (30–60 $\mu g \cdot kg^{-1} \cdot min^{-1}$) after coronary artery bypass. The metabolic or ECG signs of myocardial ischemia that developed in some patients during adenosine infusion could not "have occurred even in the absence of adenosine."

Sven-Erik Ricksten, MD, PhD
Department of Anesthesia and Intensive Care
Sahlgrens Hospital
S-413 45 Goteborg
Sweden

References

1. Zäll S, Milocco I, Ricksten S-E. Effects of adenosine on myocardial blood flow and metabolism after coronary artery bypass surgery. Anesth Analg 1991;73:689–5.
2. Lowenstein E, Reiz S. Effects of inhalation anesthetics on systemic hemodynamics and the coronary circulation. In: Kaplan JA, ed. Cardiac anesthesia. 2 ed. Volume 1. Philadelphia: WB Saunders, 1987:3–35.
3. Smith RC, Leung JM, Mangano DT. Postoperative myocardial ischemia in patients undergoing coronary artery graft surgery. Anesthesiology 1991; 74:464–73.
4. Knight AA, Hollenberg M, London MJ, et al. Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 1988;68:681–8.
5. Leung JM, Hollenberg M, Mangano DT. Prognostic significance of ST-segment elevation in CABG surgery. Anesthesiology 1991;75(Suppl): A84.
6. Häggmark S, Hogner P, Östman M, et al. Comparison of hemodynamic, electrocardiographic, mechanical and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. Anesthesiology 1989;70:19–25.
7. Torsell L, Ekeström S, Sollevi A. Adenosine-induced increase in graft flow during coronary bypass surgery. Scand J Thorac Cardiovasc Surg 1989;23:235–9.

General Anesthesia and Toxemia of Pregnancy

To the Editor:

A recent study by Ramanathan et al. (1) typifies a major problem encountered when interpreting, and even more importantly, when drawing conclusions regarding patient management from studies comparing the effects of general and regional anesthesia on perioperative hemodynamics and the stress response.

Before accepting their conclusions, their specific anesthetic techniques must be closely scrutinized. Given the underlying patient disease, preeclampsia, epidural anesthesia was administered with what might be considered elegant attempts at delivering the optimal anesthetic. For example, fluids were given intravenously, no epinephrine was used with the local anesthetic, and an anesthetic level was chosen sufficient to provide excellent analgesia.

The general anesthesia group, on the other hand, did not receive an anesthetic optimally designed to minimize the physiologic impact of either preeclampsia or a major operative procedure. The amount of fluids given intravenously was not described, despite evidence that fluid should be administered with vasodilator therapy in toxemics (2). "General anesthesia" was induced with what has come to be the universal dose of 4 mg/kg of thiobarbiturate. This dose is known to result in light anesthesia, which intuitively will result in hypertension and a stress response occurring with intubation and operation. Three articles were referenced as justification for this fixed dose. Two of the articles (3,4) did not even refer to a fixed 4-mg/kg dose nor were dose-response studies. Kosaka et al. (5) state that "total dosage should probably lie in the range of 4–7 mg/kg" and that their data are "not meant to imply that [even] 8 mg/kg is an absolute maximum dose not to be exceeded under any circumstances." The F_{IO_2} was 0.50 before delivery, which negates one potential advantage of endotracheal anesthesia—the ability to deliver 100% oxygen. Finally, only very small subanalgesic doses of fentanyl were used after delivery of the infant.

If one's goal is to optimize the general anesthetic technique for preeclampsia, (a) intravascular volume should be restored before induction of anesthesia, (b) 100% oxygen should be administered before delivery, and, most impor-

tantly, (c) deep levels of anesthesia and adequate analgesia should be attained.

The time has come to critically evaluate how the "general anesthetic" is being administered in toxemic patients. General anesthesia for cesarean section is not one unchangeable generic entity, just as epidural anesthesia is not; both should be dynamic techniques "tailor-made" to specific circumstances. Until studies are performed that take these considerations into account, it is premature to compare "general" to "epidural" anesthesia in any patient group, including patients with toxemia of pregnancy.

Andrew P. Harris, MD
Nelson 2/OB Anesthesia
The Johns Hopkins Hospital
Baltimore, MD 21205

References

1. Ramanathan J, Coleman P, Sibai B. Anesthetic modification of hemodynamic and neuroendocrine stress responses to cesarean delivery in women with severe preeclampsia. Anesth Analg 1991;73:772–9.
2. Groenendijk R, Trimbos JBMJ, Wallenburg HCS. Hemodynamic measurements in preeclampsia: preliminary observations. Am J Obstet Gynecol 1984;150:232–6.
3. Finster M, Mark LC, Morishima HO, et al. Plasma thiopental concentrations in the newborn following delivery under thiopental–nitrous oxide anesthesia. Am J Obstet Gynecol 1966;95:621–9.
4. Christensen JH, Andreasen F, Jansen JA. Pharmacokinetics of thiopental in caesarean section. Acta Anaesthesiol Scand 1981;25:174–9.
5. Kosaka Y, Takahashi T, Mark LC. Intravenous thiobarbiturate anesthesia for cesarean section. Anesthesiology 1969;31:489–506.

In Response:

We thank Dr. Harris for his interest in our study (1) and would like to respond to his comments one by one.

First, Dr. Harris states that the induction dose of thiopental of 4 mg/kg used in our study is inadequate. He suggests that with a larger dose of thiopental to produce "deep" anesthesia, one can prevent the vascular pressor and the hormonal responses to tracheal intubation in women with severe preeclampsia. This suggestion is attractive and seems like a simple solution. However, having dealt with several women with severe preeclampsia, we believe that there are no simple solutions or easy answers, and administration of general anesthesia to such patients can be difficult and complicated. We agree with Dr. Harris that the studies by Finster et al. (2) and Christensen et al. (3) quoted in our article are not dose-response studies. We are not aware of any dose-response studies with thiopental or any other drugs to induce anesthesia in women undergoing cesarean delivery, and we are not sure if such studies are feasible. However, we believe that the findings from the above studies are extremely important and pertinent to our investigation. For example, Christensen et al. (3) administered intravenous thiopental to healthy women undergoing cesarean sections in a graded manner, ie, 200 mg initially, followed by 50 mg every 20 s until the ciliary reflex disappeared. They found that compared with nonpregnant women, the average induction dose of thiopental in pregnant women was significantly lower (3.53 ± 0.47 vs 5.43 ± 0.64 mg/kg, $P < 0.001$). The induction doses of thiopental (range 2.6–4.39 mg/kg) and the serum concentrations (range 4.30–33.7 μg/mL with a mean of 17.1 μg/mL) showed wide variability among patients. Furthermore, there was no correlation between the induction dose and serum concentration of thiopental. In other words, when we decide to use a large dose of thiopental to obtain "deep" anesthesia, what end-point should one look for? Obviously one cannot empty the whole syringe of thiopental and hope that the arterial blood pressure would not increase after tracheal intubation? In addition, the terminal half-life of thiopental in the neonates was significantly longer compared with the levels in the mothers and nonpregnant women. In a compromised fetus, this may even be more prolonged. With the available data, we believe that the use of large doses of thiopental to prevent hypertensive response in severe preeclampsia is unreliable and probably detrimental to both the mother and fetus. In our study, instead of using higher doses of thiopental, we pretreated all patients in the general anesthesia group with antihypertensive drugs commonly used in preeclamptics.

Second, Dr. Harris suggests that 100% oxygen should be delivered instead of 50% oxygen and nitrous oxide. It is well documented that increasing maternal inspired oxygen concentration significantly increases umbilical venous and arterial Po_2 as well as oxygen content (4). However, this practice requires the use of a high concentration of a potent inhaled anesthetic before the delivery of the infant. Piggott et al. (5) studied 200 women undergoing cesarean section who were randomly allocated to receive either 50% nitrous oxide in oxygen or 100% oxygen and 1%–1.5% isoflurane. These authors found significantly higher umbilical venous Po_2, but other values such as umbilical arterial blood gas values remained similar. In their study, of the 200 patients studied, only five were preeclamptic and only one of them received 100% oxygen and isoflurane. Therefore, no conclusions can be drawn from the study regarding the maternal/neonatal effects of a high concentration of isoflurane and 100% oxygen in severe preeclampsia. It is doubtful if the use of isoflurane will attenuate the hypertensive response to tracheal intubation as it is administered after tracheal intubation. Furthermore, it can cause neonatal depression.

Third, Dr. Harris comments that we administered inadequate anesthesia after the delivery of the baby. This is not true. After the delivery, we increased the concentration of nitrous oxide and administered fentanyl in 50–100-μg increments as required, up to a total dose of 250–500 μg. Although we did not mention it in our paper, the average total dose of fentanyl in the group of 10 patients receiving general anesthesia was 360 ± 75 μg (mean ± SD).

Fourth, we do not routinely administer large volumes of fluids intravenously before the induction of general anesthesia in women with severe preeclampsia. As stated in our paper, central venous pressure was monitored in 19 patients and pulmonary capillary wedge pressure in the remaining two women, and administration of crystalloids was adjusted according to central venous pressure and/or pulmonary capillary wedge pressure values.

We agree with Dr. Harris that anesthesia should be tailor-made to specific circumstances. However, it is important that protocols for clinical investigations should be

designed based on data from scientific studies and not on anecdotes and unpublished observations.

Jaya Ramanathan, MD
Phyllis Coleman, RN
Baha Sibai, MD
Departments of Anesthesiology and Obstetrics and Gynecology
The University of Tennessee, Memphis
877 Jefferson Avenue
Memphis, TN 38103-2897

References

1. Ramanathan J, Coleman P, Sibai B. Anesthetic modification of hemodynamic and neuroendocrine stress responses to cesarean delivery in women with severe preeclampsia. Anesth Analg 1991;73:772–9.
2. Finster M, Mark LC, Morishima HO, et al. Plasma thiopental concentrations in the newborn following delivery under thiopental–nitrous oxide anesthesia. Am J Obstet Gynecol 1966;95:621–9.
3. Christensen JH, Andreasen F, Jansen JA. Pharmacokinetics of thiopental in caesarean section. Acta Anaesthiol Scand 1981;25:174–9.
4. Ramanathan S, Gandhi S, Arismendy J, et al. Oxygen transfer from mother to fetus during cesarean section under epidural anesthesia. Anesth Analg 1982;61:576–81.
5. Piggott SE, Bogod DG, Rosen M, et al. Isoflurane with either 100% oxygen or 50% nitrous oxide in oxygen for caesarean section. Br J Anaesth 1990;65:325–9.

Venous Air Embolism During Spinal Instrumentation and Fusion in the Prone Position

To the Editor:

We read with interest the recent report by Albin and coworkers regarding venous air embolism (VAE) during laminectomy in the prone position (1). The actual incidence of VAE during spinal surgery is unknown, in part because complete monitoring for VAE, including a precordial Doppler, is not routinely performed in these patients. Massive VAE during spinal fusion has been rarely reported (1–3). We have observed two additional cases of VAE occurring during spinal instrumentation in the prone position on the Tower table, one of which was fatal. Monitoring included mass spectrometry, as well as arterial and central venous pressure (CVP). In the first case, a junctional rhythm and hypotension were noted during sublaminar wire placement. No air was present upon aspiration of the CVP; resuscitation was unsuccessful. Autopsy revealed air in the cardiac vessels and right ventricular outflow tract and a patent foramen ovale. In the second case, the surgeon reported air bubbles emerging from the spinous processes during decortication. Fifteen milliliters of air was aspirated from the CVP during resuscitation, and the patient recovered uneventfully.

These cases of hemodynamically significant VAE during spinal fusion support the recommendations made by Albin et al. (1) and Lang et al. (2) for increased vigilance for VAE in these patients. However, some modifications from techniques used in sitting cases may be desirable or necessary. In our institution, we routinely place a single-lumen CVP catheter for intravascular fluid management and confirm its position radiographically in the postoperative period. In the prone patient, the ideal location for a CVP catheter for treatment of VAE may be at the inferior vena cava–right atrial junction. Securing a precordial Doppler over the right atrium in the presence of chest rolls or Tower table supports is difficult. The use of nitrous oxide in patients at risk for VAE is controversial. Losasso et al. (4) reported no increase in the incidence or severity of VAE during sitting craniotomy in patients receiving nitrous oxide. However, these patients were monitored with a precordial Doppler and nitrous oxide was discontinued immediately upon Doppler detection of VAE. For spinal surgery, we generally administer nitrous oxide in concentrations ≤50%. Monitoring of spinal cord integrity is routine in our institution; total avoidance of nitrous oxide during these cases would necessitate increased concentration of the volatile anesthetics, resulting in attenuation of somatosensory evoked potential waveforms and an increase in the amount of time required to perform a "wake-up" test.

Mass spectrometry or capnography are noninvasive and sensitive monitors for VAE and should be part of routine monitoring during these cases. Early detection and rapid intervention is critical to the termination of air entrainment.

In summary, two additional cases of hemodynamically significant VAE during spinal fusion are reported. Until the true incidence of VAE in these cases is known, increased vigilance and monitoring are advocated. A prospective study is needed to clarify this issue.

Terese T. Horlocker, MD
Denise J. Wedel, MD
Roy F. Cucchiara, MD
Department of Anesthesiology
Mayo Clinic
200 First Street SW
Rochester, MN 55905

References

1. Albin MS, Ritter RR, Pruett CE, Kalff K. Venous air embolism during lumbar laminectomy in the prone position: report of three cases. Anesth Analg 1991;73:346–9.
2. Lang SA, Duncan PG, Dupuis PR. Fatal air embolism in an adolescent with Duchenne muscular dystrophy during Harrington instrumentation. Anesth Analg 1989;69:132–4.
3. Frankel AH, Holzman RS. Air embolism during posterior spinal fusion. Can J Anaesth 1988;35:511–4.
4. Losasso TJ, Muzzi DA, Black S, Cucchiara RF. The risk of nitrous oxide in sitting neurosurgical patients: a prospective randomized study. Anesthesiology 1989;71:A1137.

To the Editor:

Dr. Albin and colleagues present a well-documented case of VAE during radical retropubic prostatectomy (1). The authors discuss the fact that multiple episodes of Doppler-detected VAE occurred without the ability to aspirate air through the CVP catheter (although 20 mL of air was aspirated on one occasion). They suggest that this inability to aspirate air may have been related to the sensitivity of the Doppler and the time lag between the moment of Doppler activation with an auditory signal and manual aspiration of the CVP catheter ("small volumes of air may pass the tip of the central line before aspiration occurs and the bubbles then enter the right atrium").

I would like to suggest another factor that might have played an important role in the inability to aspirate air from the CVP catheter. The catheter used for air aspiration was positioned at the junction of the right atrium and superior vena cava (as confirmed by a radiograph). The prior study

by Bunegin et al. (2), which suggested that this was the optimal catheter position for aspiration of VAE, was conducted in a heart model with air injected into the superior vena cava. In these experiments, the model heart was maintained in either a horizontal or "head up" position (frontal inclinations of 60°, 80°, and 90°). In contrast to these model simulations, the patient in the case report was positioned in a head-down position, and air entry into the heart was via the inferior vena cava. Air entering the heart at the junction of the inferior vena cava and right atrium might therefore be in a position superior to the CVP catheter tip, and less amenable to aspiration via the catheter due to gravitational effects. Have the authors performed any in vitro model studies (similar to the prior study by Bunegin et al.) under these conditions (ie, air entry via the inferior vena cava and frontal plane inclination below the horizontal position)?

Terry W. Latson, MD
Department of Anesthesiology
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, TX 75235–8894

References

1. Albin MS, Ritter RR, Reinhart R, Erickson, Rockwood A. Venous air embolism during radical retropublic prostatectomy. Anesth Analg 1992; 74:151–3.
2. Bunegin L, Albin MS, Helsel PE, Hoffman A, Hung TK. Positioning the right atrial catheter: a model for reappraisal. Anesthesiology 1981;55: 343–8.

In Response:

We appreciate the remarks of Horlocker and colleagues and that of Latson concerning our recent paper (1). Although he was not an author on the original paper, we have asked Bunegin to participate in these comments because of his expertise in air bubble distribution and rheology.

One of the critical problems in dealing with VAE in the prone position relates to its rapid diagnosis, and one can safely say that the precordial Doppler appears to be the most sensitive monitor available at this point in time (2,3). Although it might be difficult to position the Doppler with the patient in the prone position, we have been able to deal with this problem successfully. In the event bolsters are used, we secure the precordial Doppler in place, covering it with an ample supply of 4×4-in. sponges covered over with elastoplast and preceded with benzoin or other adhesive. When the Tower table is used, the Doppler probe is surrounded by a cushion of foam rubber and taped in place.

Although we believe that the lag time between Doppler air bubble detection and catheter aspiration can be a factor in explaining the inability to aspirate air, Dr. Latson may be correct in thinking that the volume of air obtained from catheter aspiration may be decreased in the prone position because of gravitational layering of air above the catheter tip out of range of the cone of aspiration. We have carried out bench experiments (unreported) with the right atrial model in the horizontal (supine) plane that suggest a reduction in aspiration efficiency occurs in both the single-orificed and multiorificed catheters. This appears to be primarily due to the sinking of the higher density (relative to blood) catheters, while bouyancy keeps the air emboli floating near the upper surface of both the superior vena cava and the right atrium. Limited success in aspirating air in this position was observed using a balloon-tipped single-orifice catheter. After balloon inflation with 0.75–1.00 mL of air, the catheter floated to the upper surface, positioning itself among the air bubbles and allowing for better aspiration.

Besides the fact that routine monitoring for VAE is usually not performed during spinal surgery in the prone position, our lack of knowledge of the actual incidence of VAE has also been influenced by the malpractice crisis. In general, outcomes involving serious morbidity or death that are in the process of litigation are now rarely reported in the medical literature, even when the legal process has been terminated for a considerable period of time. In talks and telephone conversations with anesthesiologists in many parts of the United States subsequent to the publication of this paper, the senior author (M.S.A.) was astounded to find that the problem of VAE in the prone position during spinal surgery resulting in serious outcomes was encountered by many of our colleagues during the past decade and never reported in the literature. It is important that this problem be addressed as we are being lulled into a false sense of security, resulting in a skewed incidence rate of these complications.

Maurice S. Albin, MD, MSc (Anes)
Richard R. Ritter, MD
Leon Bunegin, BS
Department of Anesthesiology
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284

References

1. Albin MS, Ritter RR, Pruett CE, Kalff K. Venous air embolism during lumbar laminectomy in the prone position: report of three cases. Anesth Analg 1991;73:346–9.
2. Fong J, Gadella R, Pierce MK, Druzin M. Are Doppler-detected venous emboli during cesarean section air emboli? Anesth Analg 1990;71:254–7.
3. Chang J, Albin MS, Bunegin L, Hunt T. Analysis and comparison of venous air embolism detection methods. Neurosurgery 1980;7:135–41.

An Aid to Oral Intubation in Patients With Potential Cervical Spine Injuries

To the Editor:

The recent review article by Hastings and Marks presents a refreshing and sensible approach to the airway management of patients with potential cervical spine injuries (1). In line with most British anesthetists, we would also recommend direct laryngoscopy and oral intubation, with the head stabilized in the neutral position, for patients with potential cervical spine injury requiring immediate airway control. When the head and neck are in this position, the glottis tends to be more anterior and at laryngoscopy complete, or even partial, exposure of the cords may be impossible. Under these circumstances an excellent, simple aid to intubation, not mentioned by the authors, is the gum

ANESTH ANALG
1992;75:141–56

elastic bougie (Eschmann, England) (2,3). This device is commonly used in the United Kingdom, but would seem to be less popular in North American practice. The distal 2 cm of the bougie is angled at about 45°, and if this is guided behind and adjacent to the epiglottis, it will invariably pass through the cords into the trachea. The tracheal tube can then be "rail-roaded" over the bougie down into the trachea. Endotracheal placement of the bougie is confirmed if it is felt to (a) bounce over tracheal rings, (b) rotate as it enters a main bronchus, or (c) come to a stop within the chest as it reaches the small bronchi during gentle insertion (4,5). Correct placement of the tube in the trachea must be confirmed in the usual manner, preferably by capnography. A study that we have just completed has shown that use of the gum elastic bougie during routine intubation adds, on average, only 10 s to the overall time taken for the procedure. If the bougie was used routinely as an aid to the oral intubation of patients with potential cervical injuries, it would be unnecessary to expose the cords, and movement of the cervical spine would be minimal.

Jerry P. Nolan, FCAnaes
Michael E. Wilson, PhD, FFARCS
Department of Anaesthetics
Royal United Hospital
Combe Park
Bath BA1 3NG
United Kingdom

References

1. Hastings RH, Marks JD. Airway management for trauma patients with potential cervical spine injuries. Anesth Analg 1991;73:471–82.
2. Macintosh RR. An aid to oral intubation. Br Med J 1949;1:28.
3. Tomlinson AA. Difficult tracheal intubation. Anaesthesia 1985;40:496–7.
4. Sellers WFS, Jones GW. Difficult tracheal intubation. Anaesthesia 1986; 41:93.
5. Kidd JF, Dyson A, Latto IP. Successful difficult intubation. Use of the gum elastic bougie. Anaesthesia 1988;43:437–8.

Not All E Cylinders Were Created Equal

To the Editor:

Recently we encountered an anesthesia machine that would not roll. The machine was a North American Dräger Narkomed 2B, and the cause of the immobility was an oversized aluminum E cylinder pressing against one of the rear wheels (Figure 1).

Spun aluminum E cylinders have gained popularity because of their light weight, corrosion resistance, and ease of handling. However, for adequate strength, the aluminum cylinder walls must be thicker than standard steel cylinders. To compensate for internal volume loss, spun aluminum cylinders were originally 2 in. longer than steel cylinders (28¼ in. versus 26¼ in.) but had the same 4¼ in. outer diameter. Because the longer aluminum cylinders were unsuitable for many applications, the industry returned to manufacturing the standard 26¼-in. length and increased the outer diameter to 4⅜ in.

Installation of the longer aluminum E cylinders sometimes causes anesthesia machine immobility. Forced rolling of such a machine could shear the cylinder valve from the hanger yoke and create a substantial hazard. Some members of the compressed gas industry have referred to the longer cylinders as the edsel of compressed gas cylinders.

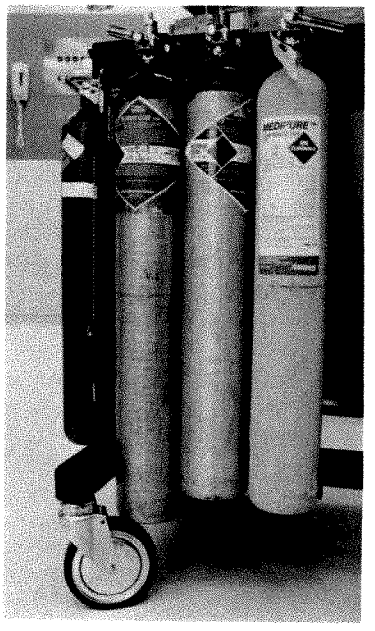


Figure 1. The oversized aluminum E cylinder on the left immobilized the rear wheel of the anesthesia machine. The center aluminum cylinder has a larger external diameter than the steel cylinder on the right.

J. Jeff Andrews, MD
Robert V. Johnston, Jr., MD
Department of Anesthesiology, E-91
The University of Texas Medical Branch
Galveston, TX 77550-2778

Anesthetic Drugs and the Emergency Department: One Teaching Institution's Response

To the Editor:

We read with interest the recent article by Cheng and colleagues regarding anesthetic drug use in the emergency department (ED) (1). We agree that anesthesia involvement to maintain quality of care and ensure appropriate drug administration in the ED is mandatory, and wish to relate our multidisciplinary response to this problem.

We held an initial meeting to determine which specific anesthetics should be routinely stocked in the ED. A protocol for each chosen drug was then developed by the ED attending staff, reviewed, and revised where necessary by an anesthesiologist, and subsequently signed by the chairmen of anesthesia and emergency medicine for incorporation into the ED's policies and procedures manual. The protocols were also standardized to include the following:

1. Statements restricting use only under the direct supervision of the ED attending physician
2. A statement for neuromuscular blocking drugs mandating that surgical control of the airway be immediately available
3. A concise list of each agent's indications and contraindications
4. Each drug's onset and duration of action
5. Unusual drug side effects (such as stimulation of secretions and emergence phenomena from ketamine)
6. Proper procedures for drug administration, including:
   a. an observable location
   b. Immediate availability of all equipment necessary for definitive airway management and resuscitation
   c. Required monitoring, with intravenous access, electrocardiogram, pulse oximetry, and supplemental oxygen as minimum standards
   d. Drug dose and mode of administration (bolus, titration to effect or maximum dose, use of "priming" technique, etc.)
   e. Use of preoxygenation, cricoid pressure, and confirmation of appropriate endotracheal tube placement using a colorimetric end-tidal carbon dioxide detector (2) for all rapid-sequence intubation techniques

To ensure rapid access to vital drug information, a one-page chart summarizing all drug doses, onsets and durations of action, and contraindications was taped to the door of the ED controlled substances lockbox containing these agents. In-service sessions for both ED physicians and nurses were subsequently held to familiarize them with the appropriate use and effects of each agent. The ED's quality improvement program has not discovered any cases of adverse patient outcome or inappropriate agent use in the 18 mo that have elapsed since these protocols were instituted.

We encourage readers to initiate similar programs within their institutions in an ongoing effort to maintain standards of care regarding anesthetic drug use in the ED.

Jeffrey S. Kelly, MD, FACEP
Earl Schwartz, MD, FACEP
The Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, NC 27157

References

1. Cheng EY, Nimphius N, Kampine JP. Anesthetic drugs and emergency departments. Anesth Analg 1992;74:272–5.
2. Anton WR, Gordon RW, Jordan TM, Posner KL, Cheney FW. A disposable end-tidal CO_2 detector to verify endotracheal intubation. Ann Emerg Med 1991;20:271–5.

Peer-Reviewed Anesthesiology Journals and Research

To the Editor:

The excellent review of anesthesiology journals by Dr. N. M. Greene (1) raises two important issues. The first is whether peer-reviewed anesthesiology journals accurately reflect the health, vigor, and scientific validity of our scientific discipline and the second is whether the amount of new, important, and valid scientific research is actually decreasing in proportion to the total amount of material published in the anesthesiology literature.

Dr. Greene asserts that the contents of peer-reviewed journals represent the cutting edge of our specialty; we must therefore rely upon these sources to keep abreast of new developments and resign ourselves to the increased time and expense required. I would argue that it is not the task of ordinary anesthesiologists to make up for the deficiencies of an ever increasing number of journals or their contents. It is surely the duty of editors to separate the wheat from the chaff to ensure that the reader is not troubled by useless and irrelevant material. By the same token I would argue that readers of journals cannot make up for the deficiencies of mediocre research programs; doctors are still poorly trained in scientific methodology and the stimulus for research is often related to promotion or tenure rather than genuine interest.

Clearly we can only individually assess the health of our specialty and keep abreast with an ever expanding research base if all the data are presented. But how may this be achieved without increasing, still further, the number of publications? I might suggest improved training, the encouragement of relevant long-term projects not necessarily linked to career status (especially multicenter studies and studies of morbidity and mortality), and the inclusion of specialists, for example, statisticians in all research programs. I would also suggest that biomedical journals be encouraged to publish information concerning the number and quality of rejected papers and that papers that would otherwise be rejected are published, without modification, with a critical review in a special section or edition. This latter approach might discourage the submission of poor research, educate potential researchers, and provide a little light amusement (Dear Dr. Lewis thank you for your interesting article, we intend to publish it in next month's "rejected" section). Finally I would suggest that authors remain anonymous until a given article is finally accepted or rejected for publication, thus helping to eliminate bias induced by knowledge of the authors' previous research or status.

Dr. Greene's comments should alert the academic community that all may not be well; history has a habit of repeating itself. Jonathan Swift's allegorical account of scientific research, depicted in Gulliver's visit to the grand Academy of Lagado in the land of Balnibarbi (2), was based on a visit in 1710 to the Royal Society in London. Today we view the antics of the scientists in *Gulliver's Travels* with some amusement and give the book to our children to read. I hope that future generations of intellectuals will not regard us in the same light.

Ian H. Lewis, MB, BS, MRCP, FFARCS
Department of Anesthesiology
IG 323, University Hospital
Box 0048
1500 East Medical Center Drive
Ann Arbor, MI 48109

References

1. Greene NM. Anesthesiology journals, 1992. Anesth Analg 1992;74:116–20.
2. Swift J. Gulliver's travels. London: Penguin Classics, 1985:223–41.

In Response:

Dr. Lewis presents us with a rich smorgasbord of comments, complaints, and recommendations. Those most deserving of response include:

The comment to the effect that "it is surely the duty of editors to separate the wheat from the chaff" in deciding what to accept for publication is a truism. In fact, as suggested in the article Dr. Lewis is commenting upon, failure of editors to recognize this responsibility is one of the reasons why there are so many articles in today's plethora of anesthesia journals that can best be characterized as space-occupying lesions or just plain shifting dullness. The author of the article being commented upon declined to quantitate this by statistical analysis and citation of data but instead elected to make the point obliquely and subtly. Too obliquely and subtly for Dr. Lewis, perhaps, but in today's litigious society in which three times more lawyers than doctors are produced, prudence, to say nothing of civility, is in order. There are many reasons why editors are remiss in this regard, reasons we need not dwell upon in writing, but certainly they include the pressure put on some editors to publish less than memorable materials rather than adhere to standards so high that an issue of their journal might contain only 50 pages.

The suggestion that authors of articles submitted for publication remain anonymous during the review process is naive. Two-thirds of the papers submitted for publication that merit publication represent a continuum of articles coming from established, productive research programs. One does not need a title page to know where they come from. If in doubt, one has only to check the references cited. The remaining third of the papers submitted for publication that warrant publication come from first-time or infrequent authors who remain functionally anonymous because few if any reviewers know them.

The plea for auctorial anonymity also includes an element of offensiveness. It implies that the intellectual integrity of reviewers is so fragile as to yield to the sin of bias simply because the name and origin of the paper under consideration are known to the reviewer. One need not impugn the honesty and objectivity of reviewers of papers as a weakness inherent in the peer-review process. Also, of course, one of the responsibilities of editors-in-chief is to monitor critiques of reviewers and to eliminate those reviewers who produce critiques vapid, hostile, or biased. Such quality control is most readily achieved by relying upon a restricted number of reviewers of demonstrable ability and proven objectivity and reliability (eg, an editorial board), rather than covering the countryside with requests for manuscript reviews from inexperienced consultants even if they happen to be expert in the topic involved. An expert is not always necessarily a good reviewer.

Finally, this reader is not accustomed to being left speechless but he finds he is totally aphasic when trying to respond to the suggestion that rejected papers be published, along with reasons for rejection, in, presumably a new anesthesia journal, the "Journal of Inadequate Papers" (JIP). Perhaps we can leave the satire to Jonathan Swift.

Nicholas M. Greene, MD
Department of Anesthesia
Yale University School of Medicine
New Haven, CT 06510

Another Approach With the Laryngeal Mask Airway

To the Editor:

I read with interest the letter by Dr. Benumof on the use of the Brain laryngeal mask airway (LMA) to facilitate fiberscopic intubation (1).

I too use the LMA as a routine in the management of patients in whom it may be difficult to visualize the larynx conventionally. I reserve the technique for those patients who would not otherwise be candidates for rapid-sequence induction and cricoid pressure.

I begin by a conventional mask gaseous induction using isoflurane or halothane in oxygen. Once the patient is judged to be "deep" enough to tolerate an airway, I insert the LMA and complete the spontaneous ventilation induction. I then insert the fiberscope "loaded" with a 6.0 uncuffed endotracheal tube (ETT) through the fiberscope swivel connector (Portex) and into the LMA. I introduce the scope and ETT in the manner described by Dr. Benumof, while maintaining anesthesia through the LMA. After intubation, the breathing system can then be connected to the ETT to continue anesthesia before the final step, which is to change the small ETT for another of the required diameter. For this purpose I use a gum elastic bougie (barely long enough) or a "bicycle cable," which is passed through the 6.0 ETT before the ETT and LMA are removed together. Reintubating over the bougie is facilitated by a 90° counterclockwise twist of the ETT.

The advantages of this technique are that "no bridges are burned" as spontaneous ventilation is maintained, anesthesia can be continued through the LMA until the moment the trachea is intubated, and an appropriate-sized ETT is used for the duration of the surgery.

Unlike Dr. Benumof I retain the ETT in the trachea in cases of difficult intubation until I am satisfied that the patient is awake and protective reflexes have returned.

I share Dr. Benumof's view that there is a role for the LMA in the management of a difficult intubation but would add that experience is needed with the technique and that safety may be enhanced by maintaining spontaneous ventilation until the airway is secured with an endotracheal tube.

David I. Thomas, FFARCS
Department of Anesthesia
University of Texas Medical Branch
Galveston, TX 77550

Reference

1. Benumof JL. Use of the laryngeal mask airway to facilitate fiberscope-aided tracheal intubation. Anesth Analg 1992;74:313–5.

Section Editor
Norig Ellison

Book Reviews

Lecture Notes on Anaesthetics

John N. Lunn. Boston, Massachusetts: Blackwell Scientific, 1991, 149 pp, $29.95.

The fact that this text is in its fourth edition since 1979 suggests the success of previous editions. As its title implies, the text does read as if it were based on lecture notes prepared for medical students. An introductory chapter on "Why Anesthesia?" contains such philosophical remarks as "surgical operations are best done as a result of cooperation between equal partners" and "there are fewer diagnoses to be made in anesthesia than in general medicine, but the time available for making the diagnoses is much briefer." Dr. Lunn's readable style is this book's greatest forte. It makes the entire text more enjoyable for the reader and makes this text something that a medical student could assimilate in a very short time. Individual chapters cover subjects such as preoperative assessment, resuscitation, applied pharmacology, monitoring, coma, applied physiology, local and regional anesthesia, and equipment. The author avoided making the content as inclusive as the introductory texts or larger reference works on anesthesiology written in the United States. The lack of references might limit further reading for the inquisitive student. Variations in terminology, drugs, and even references to monitoring, give *Lecture Notes on Anaesthetics* a decidedly British flavor, which should make it more popular among medical students in the United Kingdom.

Ronald J. Faust, MD
Mayo Medical School
Rochester, Minnesota

Moc Hoa

Larry P. Kammholz. Oshkosh, Wisconsin: Starboard, 1990, 103 pp.

Viet Nam—the name still stirs dark memories, primitive passions and visceral feelings of guilt, remorse, anger, and hate. But there were those who assumed great risks and faced daunting danger to serve the wounded and ill and to save lives, those of American and allied military personnel, those of the enemy, and importantly, those of the innocent—men, women, and children, who could not run or hide, and who had no option but to stay in their own country and suffer the blows of their own countrymen, and those who would save them from their countrymen. The role of the military physician in Viet Nam has received scant attention, either in the contemporary press or in later reviews. Television presentations have been pretentious nonsense and insulting to those who served in Southeast Asia.

In *Moc Hoa*, Larry Kammholz, has attempted to rectify this situation and shine a light into the one of the dark corners of military medicine in Viet Nam, but with mixed results. He served as Medical Director of a MILPHAP (Military Provincial Hospital Assistance Program) team in the village of Moc Hoa in Kien Tuong Province, west of Saigon and near the Cambodian border in the Plain of Reeds. He presents a diary of his presence in Viet Nam in 1966–1967 with the amateurish intensity of one undergoing a wrenching emotional and physical experience, spewing forth unrelated facts, ideas, events, jumbling them all together and then tumbling them out before us. Sentences do not flow; they stumble along falling all over each other. The accompanying photographs add little to the text.

The book is superficial. Dr. Kammholz expresses some interest in the Vietnamese people, but never gets beyond the obvious. It is impossible also to discern his own concepts of what he did and why, and the importance of his presence. Perplexedly, he writes repeatedly of contemptible deeds committed by various military groups and personal associates, and then casually absolves them of all blame, explaining them as aberrations in their otherwise praiseworthy performance. Consistency is not his strength. Battle scenes are depicted in the WOW! GOLLY! genre best left to comic books.

Amateurish, inconsistent, perplexing, frustrating, annoying, and yet, real. For those who were there, a reminiscence. For those who were not, a realistic depiction of an unpleasant era. The definitive description of the medical effort in Vietnam is yet to be written; *Moc Hoa* is a starting point for those patient enough to bear with its faults.

Alexander W. Gotta, MD
State University of New York Health Science Center
Brooklyn, New York

The Design of Analgesic Clinical Trials. Volume 18 in Advances in Pain Research and Therapy

Mitchell B. Max, Russell K. Portenoy, and Eugene M. Laska, eds. New York: Raven Press, 1991, 729 pp, $128.50.

The Design of Analgesic Clinical Trials is written by authors invited by the editors for their expertise in clinical analgesic research. The book contains 32 chapters and is sponsored by the International Association for the Study of Pain,

©1992 by the International Anesthesia Research Society

ANESTH ANALG
1992;75:157–60

American Pain Society, U.S. Cancer Pain Relief Committee, and multiple corporate sponsors.

The editors intend this book as a resource for both the novice and the experienced in clinical research of analgesic drugs. The book provides information in the first section of various pain models and single or multiple design studies. The second section is aimed at studying analgesic efficacy in specific pain syndromes, and the third section deals with miscellaneous "other issues."

The book starts with a historical perspective of clinical research followed by chapters written by experts. These chapters are divided into three parts. Section I is titled "Steps in the Clinical Evaluation of an Analgesic" and contains the following chapters: Phase I studies, experimental pain models, single-dose analgesic comparisons, the VAS relief scale, multidose short-term analgesic studies, multidose analgesic studies in chronic pain models, and N of 1 trials. The chapters in this section provide basic information for the novice, such as definition and aims of Phase I studies, experimental analgesia and its limitation, common designs used in new analgesic investigation, outcome measures, and multidose and single patient studies. Most of the chapters are short (10 pages in length or less), with tables and figures appropriate to enhance the impact of the text. The chapter titled "Phase I studies" is the best written in this section and informative.

The second section titled "Designing Analgesia Studies to Meet Specific Clinical Needs," is 339 pages long and deals with numerous pain syndromes such as pain due to neuropathic conditions, cancer, low back problems, osteoarthritis, sickle cell disease, orofacial conditions, sports injuries, headache, and dysmenorrhea. Special situations such as trials in pediatric pain patients, spinal opioids, and patient-controlled analgesia are also discussed. This section is confusing to the reviewer and may be also to the novice. An attempt is made to define specific pain conditions and provide guidance in designing clinical analgesic trials. Even though the information provided in this section may be useful for that purpose, it does not help the clinician improve his basic knowledge of those pain syndromes. For the anesthesiologist, the chapters on spinal opioids and patient-controlled analgesia are most relevant. Unfortunately, it does not provide any new information, and in fact better and more detailed material is available in other books and journals.

The third section of 178 pages contains miscellaneous material such as pharmacokinetic consideration in analgesic study design, endogenous mediators, the training of nurse observer, the FDA regulations of clinical studies, and statistical methods. Most of the chapters are well written. For the academic anesthesiologist and/or pain specialist, the chapters "Pharmacokinetic Considerations in Analgesic Study Design" and "The Food and Drug Administration's Regulation of Clinical Studies" are extremely useful and informative.

In summary, the book fills the void for the academic anesthesiologist or pain specialist. It is well written, helps the novice more than the experienced, and is mandatory for the research library of the academic departments. It unfortunately does not give enough information to the expert in the field.

P. Prithvi Raj, MD, FCAnaes
Southeastern Pain Institute
Georgia Baptist Medical Center
Atlanta, Georgia

Blood Transfusion Therapy: A Physician's Handbook, 3rd ed., 1989, 104 pp.

Blood Transfusion Therapy: An Audiovisual Program, 2nd ed., 1991, 78 slides and two tapes.

D. T. Pasciotto, ed. Arlington, Virginia: American Association of Blood Banks, $200.00 for both the Handbook and the Audiovisual Program.

This is the third edition of *Blood Transfusion Therapy* and like the previous two editions, it is a concise, referenced summary of current transfusion medicine practices. The handbook is prepared by the AABB's Component Therapy Committee and is directed toward medical as well as paramedical professionals. The book is divided into five sections that include blood components, plasma derivatives, transfusion practices, hemostatic disorders, and transfusion reactions. Each section not only provides educational material, but also practical instruction to guide transfusion management decisions. The handbook comes in a convenient pocket size, so that it may be easily referred to when making initial preoperative anesthesia evaluations and would also be readily accessible as a reference source in the operating room.

In the sections that discuss blood components and plasma derivatives, a short description is provided of each specific component or derivative followed by indications, contraindications and precautions, and dose and administration of each component or derivative. The section on transfusion practices covers areas such as autologous transfusion, emergency transfusion, massive transfusion, and two areas not covered in previous editions, management of alloimmunization and transplantation. Although the discussions are consistently brief, references are provided as well as a list of recommended readings when further investigation is necessary.

Transfusion-transmitted disease is covered briefly under the transfusion reactions section. Given the attention to this area in recent years and concern generated, more coverage of this topic is deserved. In addition, the publication of this handbook is prior to the discovery of the hepatitis C virus (HCV) and the subsequent testing of blood and components for hepatitis C antibody (anti-HCV). A timely discussion of this topic is thus lacking.

The second edition of *Blood Transfusion Therapy: An Audiovisual Program*, was published in 1991 and is based on the handbook. Included in the program are slides, an audio tape, and a booklet. Similar to the handbook, the audiovisual program is also directed toward both medical and

paramedical professionals and is designed to review the principles and practices of transfusion medicine. The color slides provided are descriptive and formatted well. They may be used in combination with the audio tape for a readily available lecture or discussion on this topic. The booklet provided contains black-and-white illustrations of the slides along with the verbatim script of the audio tape, thus allowing for individualized study or review.

The program is divided into the same five sections as the handbook. Missing in the audiovisual program, although touched upon briefly in the handbook, is a discussion of the use of type and screen to more effectively use the supply of banked blood. Similar to the handbook, more attention could have been devoted to the discussion of transfusion-transmitted disease. The audiovisual program does, however, discuss the discovery of the hepatitis C virus and the ability to test blood and components for the virus (anti-HCV).

In summary, both the handbook and the audiovisual program provide a quick reference source for information related to transfusion therapy. It is not a complete discussion or reference source for this topic, but it is not intended to be. They instead fulfill their goal of furnishing a concise description of the practice of transfusion medicine in an informative and useful manner.

Kirk T. Benson, MD
University of Kansas Medical Center
Kansas City, Kansas

Animal Pain

Charles E. Short and Alan Van Poznak, eds. New York: Churchill Livingstone, 1992, 587 pp, $84.95.

Animal Pain represents an important new work in an area of scientific endeavor that has experienced a virtual explosion in the past three decades, with profound consequences on clinical care and the alleviation of human pain. Notwithstanding the plethora of scientific literature reporting on animal pain and animal pain models, little of this information is synthesized in convenient textbook form to make this information more accessible to the student of algology. *Animal Pain* is an effort to fill this void.

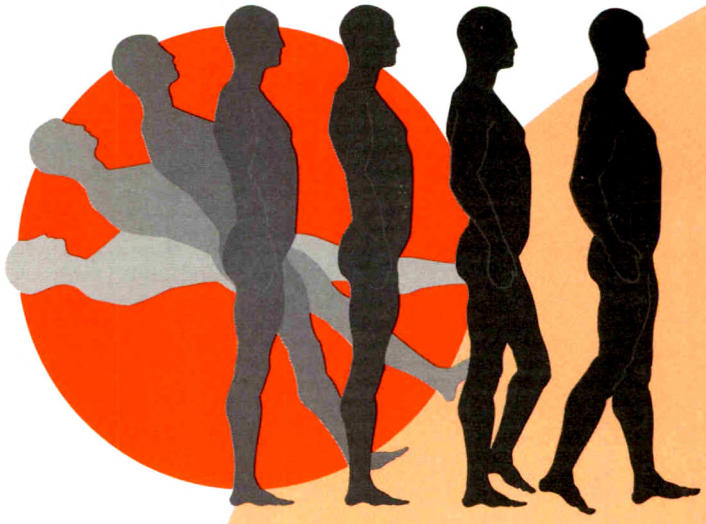
It would appear that the most immediate readership of *Animal Pain* would be students and academicians in the world of veterinary medicine, particularly those with a scientific interest in pain mechanisms. But there is a wealth of highly relevant and current information for the scientific investigator or the pain management clinician who desires to grasp the laboratory methodology that forms the scientific basis of pain medicine. The editors, Short and Van Poznak, have brought together 106 authors representing the neurosciences, clinical sciences, and veterinary medicine. The individual contributions are outstanding and quite current, with references dating as recently as 1991. The 23 chapters that comprise *Animal Pain* span a variety of topics ranging from neuropharmacology to veterinary practices. The six opening chapters deal with the neuroanatomy and neurophysiology of pain sensation, endogenous pain modulation, opioid pharmacology, and the physiologic and behavioral basis of defining animal pain. Eight chapters focus on the production of analgesia by α_2-adrenergic agents.

In keeping with the editors' goal of promoting understanding of how pain is experienced by animals, at least 10 chapters present discussions relevant to animal pain not only in the laboratory setting but in the practice of veterinary medicine and livestock management as well. This is probably one of the most unique features of *Animal Pain:* its professed concern about animal suffering and a desire to promote awareness of how pain is produced and can be alleviated in animals within a variety of settings ranging from the laboratory benchtop to the farm. Indeed, the final chapters, which focus on the detection and monitoring of pain in animals and the ethics of pain experimentation in animals, underscore the humanitarian direction that this book takes.

Notwithstanding the excellence of the individual contributions, there are some shortcomings in the final assembly of the book. Several of the chapters actually consist of two or more review articles in tandem which lack the flow or coherence of a single well-written chapter (eg, Chapters 5, 7, 8, 9, 11, and 12). Some of the chapters (eg, Chapters 10, 17, 19, and 20) are actually research papers or collections of research papers and a refereed journal of research symposium might be a more appropriate place for such papers, rather than a textbook chapter that should more properly be an authoritative review of the subject that these papers embody. Although the content of most of these papers is quite good and representative of the field, it still makes for quite a patchwork assembly to have such "chapters" sandwiched between the other "true" chapters of the book, which are indeed authoritative reviews.

There is more than a generous amount of space afforded to the discussion of α_2-adrenergic agents. This class of agents has emerged as an increasingly important class of anesthetic and analgesic agents in veterinary medicine since the introduction of xylazine and the more recent interest in detomidine and medetomidine. But there is little time devoted to other analgesic systems (5HT, GABA, NMDA, nonopioid neuropeptides) or methodologies such as chronic arthritis models, models of deafferentation, neuroma induction, and sciatic mononeuropathy induction by ligature banding (Bennett's animal model of sympathetic dystrophy which has generated a cascade of papers within the past 3 years; Pain 1988;33:87–107). Such topics would have definitely been of interest to pain investigators who utilize animal models. Electrophysiologic techniques such as WDR and STT recording are only given brief mention, even though these and other related techniques may hold the hope of supplanting the types of awake-animal behavioral studies of pain about which the editors are so concerned.

In summary, *Animal Pain* is an important new work that begins to fill a void in the pain literature and should appeal to students of veterinary medicine as well as neuroscientists and clinicians interested in algology. There are a few shortcomings in the overall construction of the book that might leave the mature scientific investigator wishing for



"The duration of action of mivacurium defines a new class of non-depolarizing neuromuscular blocking drugs."p.397

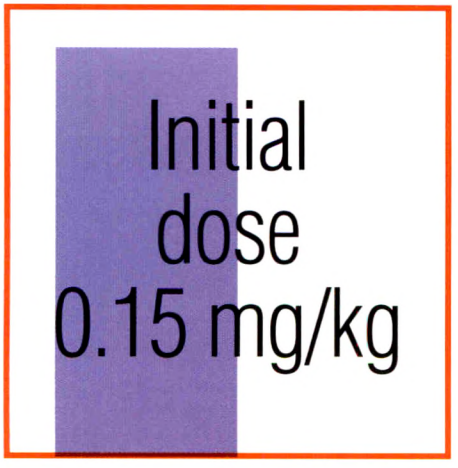
Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth*. 1989;63:393-399.

Please see full prescribing information for **M**IVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

New MIVACRON®

The first and only short

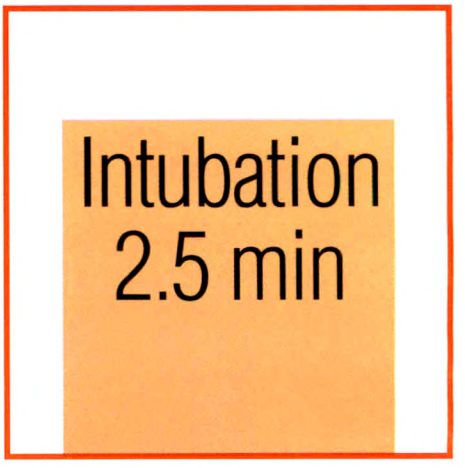
Duration of action and spontaneous recovery profile approximately one-third to one-half that of intermediate agents such as atracurium or vecuronium



Profound neuromuscular block

Recommended initial adult dose

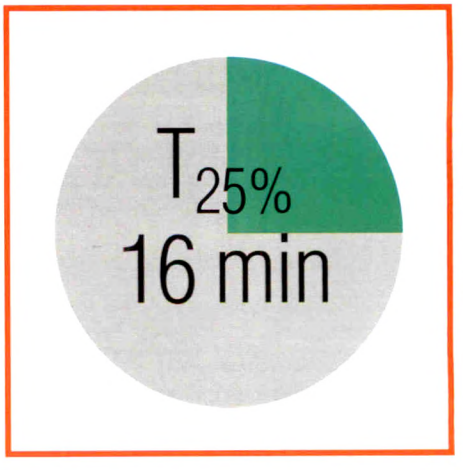
The recommended initial adult bolus dose of 0.15 mg/kg (administered over 5 to 15 seconds) provides profound neuromuscular block.



Generally good to excellent intubating conditions

Useful for routine intubation

MIVACRON provides generally good to excellent intubating conditions in 2.5 minutes at a dose of 0.15 mg/kg. Succinylcholine remains the drug of choice for rapid sequence intubation.



Short duration of action

Well-suited for short procedures

Duration of clinically effective block (time to 25% recovery of T_1) following injection of 0.15 mg/kg is 16 minutes, making **M**IVACRON excellent for short procedures.[1]

from Burroughs Wellcome Co.

acting nondepolarizer

Reduce spontaneous recovery time by up to 50% *vs* vecuronium

	Duration of continuous infusion (min)	Recovery times (min) Off-25%*	25-75%	5-95%
MIVACRON (n=25)	**86.2±5.6**	**5.7±0.3**	**6.4±0.2**	**13.6±0.6**
vecuronium (n=18)	96.8±6.6	12.7±1.3†	13.8±0.9‡	32.0±1.2‡§
atracurium (n=22)	91.3±2.9	12.5±0.6†	10.9±0.3†	26.6±0.4†

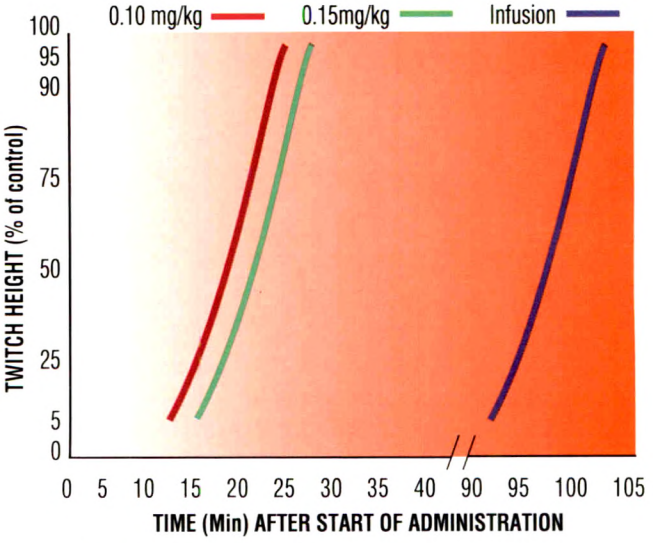
Adapted from Ali et al, p. 544.[2] *Time from discontinuation of infusion to 25% recovery. †P<0.01 atracurium or vecuronium vs MIVACRON; ‡P<0.001 vecuronium vs MIVACRON; §P<0.05 vecuronium vs atracurium.

Noncumulative

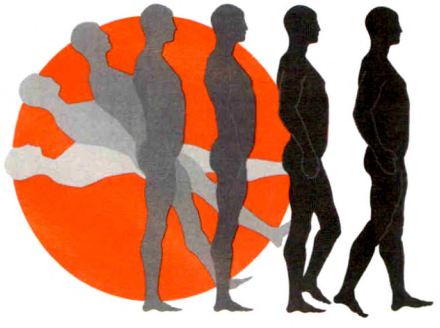
Continuous infusion of MIVACRON for up to 2.5 hours is not associated with the development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Steady-state levels of block are rapidly achieved with minimal adjustment to the infusion rate. Limited data are available on MIVACRON (a mixture of three isomers) for infusions longer than 2.5 hours.

Savarese et al found...

Fast recovery following bolus or infusion



Adapted from Savarese et al, p. 727.[3]



New MIVACRON® Injection 2 mg/mL (mivacurium chloride)

Short duration, fast recovery

Please see full prescribing information for MIVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

New MIVACRON®

Up to half the duration

Excellent cardiovascular profile at recommended doses

MIVACRON Initial Dose* (mg/kg)	% of patients with ≥ 30% changes			
	MAP		HR	
	↓	↑	↓	↑
0.07 to 0.10	0%	2%	0%	0%
0.15	4%	4%	4%	2%
0.20†	30%	0%	0%	8%
0.25†	39%	2%	0%	14%

*During opioid/N_2O/O_2 anesthesia.
†Experimental dose, in excess of the maximum recommended dose of 0.15 mg/kg.

Minimal CV effects

At the recommended initial dose of 0.15 mg/kg, cardiovascular response to **M**IVACRON is minimal. Higher doses may produce effects associated with histamine release and may result in a decrease in blood pressure in some individuals. The incidence and magnitude of these hemodynamic changes are related to size of the dose and speed of the injection. In patients with clinically significant CV disease, the initial dose of **M**IVACRON should be administered over 60 seconds.

Metabolized by plasma cholinesterase

Like succinylcholine, **M**IVACRON should be used with caution in patients with reduced plasma cholinesterase activity. In patients heterozygous for the atypical plasma cholinesterase gene, clinically effective duration may be prolonged by approximately 10 minutes. Homozygous patients (1 in 2500) are *extremely sensitive* to **M**IVACRON. **M**IVACRON should be used with great caution, if at all, in homozygous patients.

However, unlike succinylcholine, once recovery has begun, **M**IVACRON can be reversed with conventional doses of neostigmine.

Individualization of dosages

- Significant CV disease
- Obesity
- Renal or hepatic disease
- History suggesting greater sensitivity to release of histamine or related mediators

from Burroughs Wellcome Co.

half the recovery time

A nondepolarizing alternative to succinylcholine for elective outpatient surgery

	n	Time to max. block (min)*	Time to recovery of T_1=10% (min)*
succinylcholine 1.0 mg/kg	9	1.1±0.2	7.7±1.4
MIVACRON 0.15 mg/kg	8	**2.5**±0.9	**15.6**±3.4

Adapted from Caldwell et al, p.395.[1] *P<0.05 succinylcholine vs **M**IVACRON.

Caldwell et al concluded...

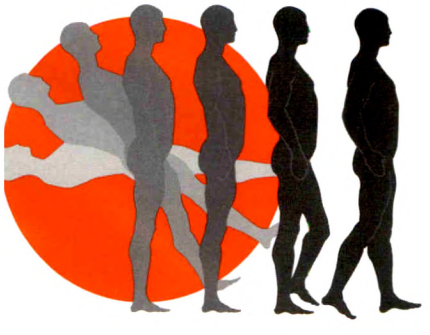
"...in those clinical situations in which rapid onset of action is not required, mivacurium is an alternative to [succinylcholine] for production of profound neuromuscular block of short duration."[p.398]

Plus...

- For use by bolus or infusion
- Ready-to-use solution
- Room temperature storage
- Available in 5 mL and 10 mL vials (2 mg/mL) and 50 mL premixed infusion bags (0.5 mg/mL)

REFERENCES

1. Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth.* 1989;63:393-399.
2. Ali HH, Savarese JJ, Embree PB, et al. Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. *Br J Anaesth.* 1988;61:541-546.
3. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology.* 1988;68:723-732.



New MIVACRON® Injection 2 mg/mL (mivacurium chloride)

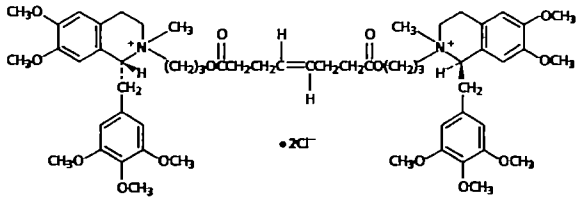
Short duration, fast recovery

Please see full prescribing information for **M**IVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

MIVACRON® INJECTION
MIVACRON PREMIXED INFUSION
(MIVACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: MIVACRON (mivacurium chloride) is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Mivacurium chloride is [*R*-[*R**,*R**-(*E*)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18. The structural formula is:



The partition coefficient of the compound is 0.015 in a 1-octanol/distilled water system at 25°C.

Mivacurium chloride is a mixture of three stereoisomers: (1*R*, 1'*R*, 2*S*, 2'*S*), the *trans-trans* diester; (1*R*, 1'*R*, 2*R*, 2'*S*), the *cis-trans* diester; and (1*R*, 1'*R*, 2*R*, 2'*R*), the *cis-cis* diester. The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers.

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. MIVACRON Premixed Infusion is a sterile, non-pyrogenic solution (pH 3.5 to 5.0; 260 mOsmol/L-measured) containing mivacurium chloride equivalent to 0.5 mg/mL mivacurium in 5% Dextrose Injection USP. Hydrochloric acid may have been added to adjust pH.

CLINICAL PHARMACOLOGY: MIVACRON (a mixture of three stereoisomers) binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: The time to maximum neuromuscular block is similar for recommended doses of MIVACRON and intermediate-acting agents (*e.g.*, atracurium), but longer than for the ultra-short-acting agent, succinylcholine. The clinically effective duration of action of the stereoisomers in MIVACRON (a mixture of three stereoisomers) is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of succinylcholine.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.06 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of doses of MIVACRON ≥ED_{95} administered over 5 to 15 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n=32) following an initial dose of 0.15 mg/kg MIVACRON and 7 to 8 minutes (range: 4 to 24, n=85) following initial doses of 0.20 or 0.25 mg/kg MIVACRON.

Volatile anesthetics may decrease the dosing requirement for MIVACRON and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration]) may decrease the effective dose of MIVACRON by as much as 25%, and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. At equivalent MAC values, halothane has little or no effect on the ED_{95} of MIVACRON, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and **Drug Interaction** subsection of PRECAUTIONS).

Table 1
Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		Time to Maximum Block[1] (min)	Time to Spontaneous Recovery[1] 5% Recovery (min)	25% Recovery[2] (min)	95% Recovery[2] (min)	T_4/T_1 Ratio ≥ 75%[3] (min)
Adults						
0.07 to 0.10	[n=47]	4.9 (2.0-7.6)	11 (7-19)	13 (8-24)	21 (10-38)	21 (10-36)
0.15	[n=50]	3.3 (1.5-6.8)	13 (6-31)	16 (9-36)	28 (16-41)	26 (15-45)
0.20	[n=50]	2.5 (1.2-6.0)	16 (10-29)	20 (10-38)	31 (15-51)	34 (19-56)
0.25	[n=48]	2.3 (1.0-4.8)	19 (11-29)	23 (14-36)	34 (22-64)	43 (26-75)
Children 2 to 12 Years						
0.11 to 0.12	[n=17]	2.8 (1.2-4.6)	5 (3-9)	7 (4-10)	–	–
0.20	[n=18]	1.9 (1.3-3.3)	7 (3-12)	10 (6-15)	19 (14-26)	18 (12-23)
0.25	[n=9]	1.6 (1.0-2.2)	7 (4-9)	9 (5-12)	–	–

[1]Values shown are medians of means from individual studies (range of individual patient values).
[2]Clinically effective duration of neuromuscular block.
[3]Data available for as few as 40% of adults in specific dose groups and for 22% of children in the 0.20 mg/kg dose group due to administration of reversal agents or additional doses of MIVACRON prior to 95% recovery or T_4/T_1 ratio recovery to ≥75%.

Administration of MIVACRON over 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of the stereoisomers in MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS and **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Interpatient variability in duration of action occurs with MIVACRON as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of MIVACRON during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery indicated that approximately 90% of the patients had clinically effective durations of block within 8 minutes of the median duration predicted from the dose-response data shown in Table 1. Variations in plasma cholinesterase activity, including values within the normal range and values as low as 20% below the lower limit of the normal range, were not associated with clinically significant effects on duration. The variability in duration, however, was greater in patients with plasma cholinesterase activity at or slightly below the lower limit of the normal range.

A dose of 0.15 mg/kg (2 x ED_{95}) MIVACRON administered during the induction of thiopental/opioid/nitrous oxide/oxygen anesthesia produced generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Doses of 0.20 and 0.25 mg/kg (3 and 3.5 x ED_{95}) yielded similar conditions in 2.0 minutes.

Repeated administration of maintenance doses or continuous infusion of MIVACRON for up to 2.5 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Limited data are available from patients receiving infusions for longer than 2.5 hours. Spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).

The neuromuscular block produced by the stereoisomers in MIVACRON is readily antagonized by anticholinesterase agents. As seen with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

In children (2 to 12 years), MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, and shorter duration of action than in adults. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 5 minutes (n=4) following an initial dose of 0.20 mg/kg MIVACRON. Recovery following reversal is faster in children than in adults (Table 1).

Hemodynamics: Administration of MIVACRON in doses up to and including 0.15 mg/kg (2 x ED_{95}) over 5 to 15 seconds to ASA Physical Status I-II patients during opioid/nitrous oxide/oxygen anesthesia is associated with minimal changes in mean arterial blood pressure (MAP) or heart rate (HR) (Table 2).

Table 2
Cardiovascular Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		% of Patients With ≥30% Change MAP Dec	MAP Inc	HR Dec	HR Inc
Adults					
0.07 to 0.10	[n=49]	0%	2%	0%	0%
0.15	[n=53]	4%	4%	4%	2%
0.20	[n=53]	30%	0%	0%	8%
0.25	[n=44]	36%	2%	0%	14%
Children 2 to 12 years					
0.11 to 0.12	[n=17]	0%	6%	0%	0%
0.20	[n=17]	0%	0%	0%	0%
0.25	[n=8]	13%	0%	0%	0%

Higher doses of ≥0.20 mg/kg (≥3 x ED_{95}) may be associated with transient decreases in MAP and increases in HR in some patients. These decreases in MAP are usually maximal within 1 to 3 minutes following the dose, typically resolve without treatment in an additional 1 to 3 minutes, and are usually associated with increases in plasma histamine concentration. Decreases in MAP can be minimized by administering MIVACRON over 30 or 60 seconds (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS).

Analysis of 426 patients in clinical studies receiving initial doses of MIVACRON up to and including 0.30 mg/kg (*i.e.*, 2 times the recommended intubating dose) during opioid/nitrous oxide/oxygen anesthesia showed that high initial doses and a rapid rate of injection contributed to a greater probability of experiencing a decrease of ≥ 30% in MAP after MIVACRON administration. Obese patients also had a greater probability of experiencing a decrease of ≥30% in MAP when dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY and the **General** subsection of PRECAUTIONS).

Children experience minimal changes in MAP or HR after administration of MIVACRON doses up to and including 0.20 mg/kg over 5 to 15 seconds, but higher doses (≥0.25 mg/kg) may be associated with transient decreases in MAP (Table 2).

Following a dose of 0.15 mg/kg MIVACRON administered over 60 seconds, adult patients with significant cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures showed no clinically important changes in MAP or HR. Transient decreases in MAP were observed in some patients after doses of 0.20 to 0.25 mg/kg MIVACRON administered over 60 seconds. The number of patients in whom these decreases in MAP required treatment was small.

Pharmacokinetics: Table 3 describes the results from a study of 9 ASA Physical Status I-II adult patients (31 to 48 years) receiving an infusion of MIVACRON at 5 µg/kg/min for 60 minutes followed by 10 µg/kg/min for 60 minutes. MIVACRON is a mixture of isomers which do not interconvert *in vivo*. The mivacurium pharmacokinetic parameters presented in Table 3 were determined using a stereospecific assay. The two more potent isomers, *cis-trans* (36% of the mixture) and *trans-trans* (57% of the mixture), have very high clearances that exceed cardiac output reflecting the extensive metabolism by plasma cholinesterase. The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The combination of high metabolic clearance and low distribution volume results in the short elimination half-life of approximately 2 minutes for the two active isomers. The short elimination half-lives and high metabolic clearances of the active isomers are consistent with the short duration of action of MIVACRON. The steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled after the infusion rate was increased from 5 to 10 µg/kg/min, indicating that their pharmacokinetics are dose-proportional.

Table 3
Stereoisomer Pharmacokinetic Parameters[1] of MIVACRON in ASA Physical Status I-II Adult Patients[2] [n=9] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* isomer	*cis-trans* isomer
Elimination Half-life ($t_{1/2}$, min)	2.3 (1.4-3.6)	2.1 (0.8-4.8)
Volume of Distribution (L/kg)	0.15 (0.06-0.24)	0.27 (0.08-0.56)
Plasma Clearance (mL/min/kg)	53 (32-105)	99 (52-230)

[1]Values shown are mean (range).
[2]Ages 31 to 48 years.

The *cis-cis* isomer (6% of the mixture) has approximately one-tenth the neuromuscular blocking potency of the

trans-trans and *cis-trans* isomers in cats. In the nine patients shown in Table 3, the volume of distribution of the *cis-cis* isomer averaged 0.31 L/kg (range: 0.18-0.46), the clearance averaged 4.2 mL/min/kg (range: 2.4-5.4), and the half-life averaged 55 minutes (range: 32-102). The neuromuscular blocking potency of the *cis-cis* isomer in humans has not been established; however, modeling of clinical pharmacokinetic-pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a two-hour infusion. In studies in which infusions of up to 2.5 hours were administered to ASA Physical Status I-II patients, the 25%-75% recovery times were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not contribute significant neuromuscular block during use for up to 2.5 hours. Limited data are available from infusions of longer duration or from patients with compromised elimination capacities (hepatic or renal failure).

Metabolism and Excretion: *Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite.* Renal and biliary excretion of unchanged mivacurium are minor elimination pathways; urine and bile are important elimination pathways for the two metabolites. Tests in which these two metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of MIVACRON.

Special Populations: The pharmacokinetics of mivacurium isomers has not been studied in the elderly or in patients with renal or hepatic disease using a stereospecific assay. The non-stereospecific, total mivacurium assay used in pharmacokinetic-pharmacodynamic studies in these populations provided preliminary evidence that reduced clearance of one or more isomers is responsible for the longer duration of action of MIVACRON seen in patients with end-stage kidney or liver disease. The data did not provide a pharmacokinetic explanation for the 15-20% longer duration of block seen in the elderly. Tables 4 and 5 summarize the pharmacodynamic results in these special populations as compared with young adults (ages 18 to 49 years). No data are available from patients with kidney or liver disease not requiring transplantation.

Table 4
Pharmacodynamic Parameters[1] of MIVACRON in ASA Physical Status I-II
Young Adult Patients and Elderly Patients During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients (18-49 years)		Elderly Patients (68-77 years)
Initial Dose	0.10 mg/kg [n=9]	0.25 mg/kg [n=9]	0.10 mg/kg [n=8]
Maximum Block (%)	98 (83-100)	100 (100-100)	99 (95-100)
Time to Maximum Block (min)	3.2 (2.0-6.0)	1.7 (1.3-2.5)	4.8 (3.0-7.0)
Clinically Effective Duration of Block[2] (min)	17 (9-29)	27 (18-34)	20 (14-26)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.

Renal: The clinically effective duration of action of 0.15 mg/kg MIVACRON was about 1.5 times longer in patients with end-stage kidney disease than in healthy patients, presumably due to reduced clearance of one or more isomers.

Hepatic: The clinically effective duration of action of 0.15 mg/kg MIVACRON was three times longer in patients with end-stage liver disease than in healthy patients and is likely related to the markedly decreased plasma cholinesterase activity (30% of healthy patient values) which could decrease the clearance of one or more isomers (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Table 5
Pharmacodynamic Parameters[1] of MIVACRON in ASA Physical Status I-II Patients and in Patients Undergoing Kidney or Liver Transplantation During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients[3]
Initial Dose	0.15 mg/kg [n=8]	0.15 mg/kg [n=9]	0.15 mg/kg [n=8]
Maximum Block (%)	99.8 (98-100)	100 (100-100)	100 (100-100)
Time to Maximum Block (min)	1.9 (0.8-3.5)	2.6 (1.0-4.5)	2.1 (1.0-4.0)
Clinically Effective Duration of Block[2] (min)	19 (12-30)	30 (19-58)	57 (29-80)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.
[3]Liver transplant patients received isoflurane without nitrous oxide.

Individualization of Dosages: DOSES OF MIVACRON SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING MIVACRON ADMINISTRATION IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

Based on the known actions of MIVACRON (a mixture of three stereoisomers) and other neuromuscular blocking agents, the following factors should be considered when administering MIVACRON:

Renal or Hepatic Impairment: A dose of 0.15 mg/kg MIVACRON is recommended for facilitation of tracheal intubation in patients with renal or hepatic impairment. However, the clinically effective duration of block produced by this dose is about 1.5 times longer in patients with end-stage kidney disease and about 3 times longer in patients with end-stage liver disease than in patients with normal renal and hepatic function. Infusion rates should be decreased by as much as 50% in these patients depending on the degree of renal or hepatic impairment (see **Renal and Hepatic Disease** subsection of PRECAUTIONS).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients.

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After recommended intubating doses of MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower MIVACRON infusion rates are recommended in these patients (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Drugs or Conditions Causing Potentiation of or Resistance to Neuromuscular Block: As with other neuromuscular blocking agents, MIVACRON may have profound neuromuscular blocking effects in cachectic or debilitated patients, patients with neuromuscular diseases, and patients with carcinomatosis. In these or other patients in whom potentiation of neuromuscular block or difficulty with reversal may be anticipated, the recommended initial dose should be decreased. A test dose of not more than 0.015–0.020 mg/kg, which represents the lower end of the dose-response curve for MIVACRON, is recommended in such patients (see **General** subsection of PRECAUTIONS).

The neuromuscular blocking action of the stereoisomers in MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used for intubation prior to the administration of these agents. If MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose should be reduced by as much as 25%, and the infusion rate reduced by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking action of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. The use of halothane requires no adjustment of the initial dose of MIVACRON, but may prolong the duration of action and decrease the average infusion rate by as much as 20% (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients receiving certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide and quinidine, longer durations of neuromuscular block may be expected and infusion requirements may be lower (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients chronically receiving phenytoin or carbamazepine, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher (see **Drug Interactions** subsection of PRECAUTIONS).

Severe acid-base and/or electrolyte abnormalities may potentiate or cause resistance to the neuromuscular blocking action of the stereoisomers in MIVACRON. No data are available in such patients and no dosing recommendations can be made (see **General** subsection of PRECAUTIONS).

Burns: While patients with burns are known to develop resistance to nondepolarizing neuromuscular blocking agents, they may also have reduced plasma cholinesterase activity. Consequently, in these patients, a test dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended, followed by additional appropriate dosing guided by the use of a neuromuscular block monitor (see **General** subsection of PRECAUTIONS).

Cardiovascular Disease: In patients with clinically significant cardiovascular disease, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS).

Obesity: Obese patients (patients weighing ≥30% more than their ideal body weight) dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight, had a greater probability of experiencing a decrease of ≥30% in MAP (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS). Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (IBW), according to the following formulas:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2
Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Allergy and Sensitivity: In patients with any history suggestive of a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma), the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **General** subsection of PRECAUTIONS).

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multi-dose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED BY CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED_{90-95} in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 6 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereoisomers in MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{95} of MIVACRON by as much as 25% (see Pharmacodynamics and Individualization of Dosages subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of MIVACRON by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{95}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neuromuscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (see Reduced Plasma Cholinesterase Activity subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomers in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRON revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of MIVACRON in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see General subsection of PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients than in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who received the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. None of the 397 adults or 63 children who received recommended doses was treated for a decrease in blood pressure associated with the administration of MIVACRON. Above the recommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see Antagonism of Neuromuscular Block). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see Drug Interactions subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

Initial Dose:

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

In patients with clinically significant cardiovascular disease and in patients with any history suggesting a greater sensitivity to the release of histamine or other mediators (*e.g.*, asthma), the dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS).

Clinically effective neuromuscular block may be expected to last for 15 to 20 minutes (range: 9 to 36) and spontaneous recovery may be expected to be 95% complete in 25 to 30 minutes (range: 16 to 41) following 0.15 mg/kg MIVACRON administered to patients receiving opioid/nitrous oxide/oxygen anesthesia. Maintenance dosing is generally required approximately 15 minutes following an initial dose of 0.15 mg/kg MIVACRON during opioid/nitrous oxide/oxygen anesthesia. Maintenance doses of 0.10 mg/kg each provide approximately 15 minutes of additional clinically effective block. For shorter or longer durations of action, smaller or larger maintenance doses may be administered.

The neuromuscular blocking action of MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used to facilitate tracheal intubation prior to the administration of these agents; however, if MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose may be reduced by as much as 25%. Greater reductions in the MIVACRON dose may be required with higher concentrations of enflurane or isoflurane. With halothane, which has only a minimal potentiating effect on MIVACRON, a smaller dosage reduction may be considered.

Continuous Infusion: Continuous infusion of MIVACRON may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial dose, an initial infusion rate of 9 to 10 µg/kg/min is recommended. If continuous infusion is initiated simultaneously with the administration of an initial dose, a lower initial infusion rate should be used (*e.g.*, 4 µg/kg/min). In either case, the initial infusion rate should be adjusted according to the response to peripheral nerve stimulation and to clinical criteria. On average, an infusion rate of 6 to 7 µg/kg/min (range: 1 to 15) may be expected to maintain neuromuscular block within the range of 90% to 99% for extended periods in adults receiving opioid/nitrous oxide/oxygen anesthesia. Reduction of the infusion rate by up to 35% to 40% should be considered when MIVACRON is administered during stable-state conditions of isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC). Greater reductions in the MIVACRON infusion rate may be required with greater concentrations of enflurane or isoflurane. With halothane, smaller reductions in infusion rate may be required.

Children:

Initial Dose: Dosage requirements for MIVACRON on a mg/kg basis are higher in children than adults. Onset and recovery of neuromuscular block occur more rapidly in children than adults (see CLINICAL PHARMACOLOGY). The recommended dose of MIVACRON for facilitating tracheal intubation in children 2 to 12 years of age is 0.20 mg/kg administered over 5 to 15 seconds. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.20 mg/kg of MIVACRON produces maximum neuromuscular block in an average of 1.9 minutes (range: 1.3 to 3.3) and clinically effective block for 10 minutes (range: 6 to 15). Maintenance doses are generally required more frequently in children than in adults. Administration of MIVACRON doses above the recommended range (>0.20 mg/kg) is associated with transient decreases in MAP in some children (see Hemodynamics subsection of CLINICAL PHARMACOLOGY). MIVACRON has not been studied in children below the age of 2 years.

Continuous Infusion: Children require higher MIVACRON infusion rates than adults. During opioid/nitrous oxide/oxygen anesthesia the infusion rate required to maintain 90% to 99% neuromuscular block averages 14 µg/kg/min (range: 5 to 31). The principles for infusion of MIVACRON in adults are also applicable to children (see above).

Infusion Rate Tables:

For adults and children the amount of infusion solution required per hour depends upon the clinical requirements of the patient, the concentration of MIVACRON in the infusion solution, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient must be considered. Tables 6 and 7 provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of MIVACRON Premixed Infusion (0.5 mg/mL) and of MIVACRON Injection (2 mg/mL).

Table 6
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Premixed Infusion (0.5 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	5	6	7	8	10	12	17	19	22	24
15	7	9	11	13	14	18	25	29	32	36
20	10	12	15	17	19	24	34	38	43	48
25	12	15	18	21	24	30	42	48	54	60
35	17	21	26	29	34	42	59	67	76	84
50	24	30	36	42	48	60	84	96	108	120
60	29	36	43	50	58	72	101	115	130	144
70	34	42	50	59	67	84	118	134	151	168
80	39	48	58	67	77	96	134	154	173	192
90	44	54	65	76	86	108	151	173	194	216
100	48	60	72	84	96	120	168	192	216	240

Table 7
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Injection (2 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	1.2	1.5	1.8	2.1	2.4	3.0	4.2	4.8	5.4	6.0
15	1.8	2.3	2.7	3.2	3.6	4.5	6.3	7.2	8.1	9.0
20	2.4	3.0	3.6	4.2	4.8	6.0	8.4	9.6	10.8	12.0
25	3.0	3.8	4.5	5.3	6.0	7.5	10.5	12.0	13.5	15.0
35	4.2	5.3	6.3	7.4	8.4	10.5	14.7	16.8	18.9	21.0
50	6.0	7.5	9.0	10.5	12.0	15.0	21.0	24.0	27.0	30.0
60	7.2	9.0	10.8	12.6	14.4	18.0	25.2	28.8	32.4	36.0
70	8.4	10.5	12.6	14.7	16.8	21.0	29.4	33.6	37.8	42.0
80	9.6	12.0	14.4	16.8	19.2	24.0	33.6	38.4	43.2	48.0
90	10.8	13.5	16.2	18.9	21.6	27.0	37.8	43.2	48.6	54.0
100	12.0	15.0	18.0	21.0	24.0	30.0	42.0	48.0	54.0	60.0

MIVACRON Premixed Infusion in Flexible Plastic Containers:

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

Instructions for Use:

1. Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired.
2. Close flow control clamp of administration set
3. Remove cover from outlet port at bottom of container.
4. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
5. Suspend container from hanger.
6. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion.
7. Open flow control clamp to expel air from set. Close clamp.
8. Attach set to intravenous tubing.
9. Regulate rate of administration with flow control clamp.

Caution: Additives should not be introduced into this solution. Do not administer unless solution is clear and container is undamaged. MIVACRON Premixed Infusion is intended for single patient use only. The unused portion of the solution should be discarded.

Warning: Do not use flexible plastic container in series connections.

MIVACRON Injection Compatibility and Admixtures:

Y-site Administration: MIVACRON Injection may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Studies have shown that MIVACRON Injection is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose in Lactated Ringer's Injection
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed
- Versed® (midazolam hydrochloride) Injection, diluted as directed
- Inapsine® (droperidol) Injection, diluted as directed

Compatibility studies with other parenteral products have not been conducted.

Dilution Stability: MIVACRON Injection diluted to 0.5 mg mivacurium per mL in 5% Dextrose Injection USP, 5% Dextrose and 0.9% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, Lactated Ringer's Injection USP, or 5% Dextrose in Lactated Ringer's Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at 5°C to 25°C (41°F to 77°F) for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of MIVACRON should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted MIVACRON should be discarded after each case.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear and colorless should not be used.

HOW SUPPLIED: MIVACRON Injection, 2 mg mivacurium in each mL.

5 mL Single Use Vials. Tray of 10 (NDC 0081-0705-44).

10 mL Single Use Vials. Tray of 10 (NDC 0081-0705-95).

MIVACRON Premixed Infusion in 5% Dextrose Injection USP, 0.5 mg mivacurium in each mL.

50 mL (in a 100 mL unit) Flexible Plastic Containers. (NDC 0081-0709-01).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418 **554053**

MIVACRON Premixed Infusion Manufactured for BURROUGHS WELLCOME CO. by Abbott Laboratories

---

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

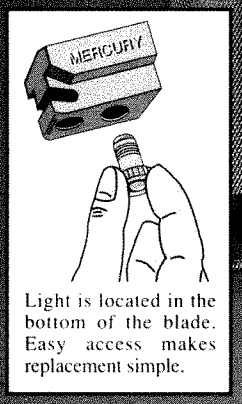
STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Wellcome Copr. © 1992 Burroughs Wellcome Co. All rights reserved. MV-Y03552

Put a MERCURY® Fiberoptic Blade

On Your Handle*



Light is located in the bottom of the blade. Easy access makes replacement simple.

The MERCURY® 2001 FIBERLIGHT® Laryngoscope Blade saves you money yet gives 400% more light, virtually eliminates flickering and fits most standard handles.*

* Standard laryngoscope handles with fittings manufactured to ISO 7376 standards.

Call or write today for a copy of our Laryngoscope Catalog

MERCURY®
MEDICAL
11300 A - 49th Street North
Clearwater, FL 34622-4800
(813) 573-0088 • 1-800-237-6418
FAX (813) 573-6040

CLIP AND RETURN FOR INFORMATION

NAME _____

TITLE _____

HOSPITAL/FIRM _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

PHONE _____

2001 FIBERLIGHT-ANESTHESIA & ANALGESIA

A Guide for Authors

Manuscripts should be sent to:

King C. Kryger, PhD
Managing Editor
Anesthesia & Analgesia
3497 Sacramento Street
San Francisco, CA 94118

Editorial Policies

Anesthesia & Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, case reports, technical communications, review articles, special articles, medical intelligence articles, editorials, book reviews, and letters to the editor. Original articles will, when possible, be assigned to one of the subspecialty sections (Ambulatory Anesthesia, Cardiovascular Anesthesia, Critical Care and Trauma, Neurosurgical Anesthesia, Obstetric Anesthesia, Pediatric Anesthesia, and Regional Anesthesia and Pain Management). All papers are reviewed by three or more referees. Acceptance is based on significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a cover letter that includes a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter. Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *The New England Journal of Medicine* 1991;324:424–8.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee. Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles, in 3000 words or less, describe clinical or laboratory investigations.
- ☐ Case reports, in 1000 words or less, describe either new and instructive cases, anesthetic techniques and equipment of demonstrable originality, usefulness, and safety, or new information on diseases of importance to anesthesia.
- ☐ Technical communications, of 1500 to 2000 words, describe instrumentation and analytic techniques.
- ☐ Review articles, of 2500 to 4000 words, collate, describe, and evaluate previously published material to aid in evaluating new concepts.
- ☐ Medical intelligence articles, of 1500 to 4000 words, usually collate, describe, and evaluate previously published material to aid in evaluating new concepts or updating old concepts or topics germane to anesthesiology.
- ☐ Special articles, of 2500 to 4000 words, describe literature, education, societies, and other topical interests of a historical or current trend in anesthesiology.
- ☐ Editorials (solicited by the Editorial Board), in 2000 words or less, comment on articles published in the journal and/or express the general policies or opinions of the Editor-in-Chief.
- ☐ Book reviews, in 1000 words or less, report on current literature available in anesthesiology.
- ☐ Letters to the editor, of 300 words or less, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double-spaced, and a title and three copies must be provided.
- ☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double- or triple-spacing (to allow room for editing) throughout, including references and table and figure legends.
- ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.
- ☐ Submit one original plus three copies of the manuscript and four sets of figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a cover letter and by letters granting permission to reproduce previously published materials or to use illustrations that may identify subjects.
- ☐ Authors should keep copies of everything submitted and all correspondence from the editorial office and its board members.

Title Page

- ☐ The title page should contain the title of the article, which should be concise but informative;
- ☐ A short running head of no more than 40 characters (count letters and spaces) placed at the bottom of the title page and identified;
- ☐ First name, middle initial, and last name of each author, with highest academic degree(s) including fellowship and board affiliations; each listed author must (a) have participated in the work to the extent that he or she could publicly defend its contents; (b) have read the manuscript before its submission for publication; and (c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication. Additional names of author(s) may not be appended after sending revised manuscript to the journal without written consent from the senior author and approval on a case-by-case basis from the Editor-in-Chief;
- ☐ Name of department(s) and institution(s) to which the work should be attributed;
- ☐ Disclaimers, if applicable;
- ☐ Name, address, telephone number, and FAX number of author responsible for correspondence about the manuscript;
- ☐ Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author;
- ☐ The source(s) of support in the form of grants.

Abstract and Key Words

- ☐ The second page should carry an abstract of not more than 150 words. (Abstracts are needed only for original articles.)
- ☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.
- ☐ Define all abbreviations except those approved by the International System of Units.
- ☐ Key (indexing) words. Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article.

Text

- ☐ The text of observational, experimental, and original articles is usually—but not necessarily—divided into sections with the following headings: Introduction, Methods, Results, and Discussion.

©1992 by the International Anesthesia Research Society

☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references and do not review the subject extensively.

☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. In the body of the text, cite the drug or chemical name followed by the generic name in parentheses and refer to the drug throughout the text by its generic name.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer-reviewed *Index Medicus* journals. Abstracts appearing only in programs of meetings are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text.

☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line)

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus*.

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus*.

☐ References must be verified by the author(s) against the original documents, and the entire list must be checked for nonduplication.

Examples:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275–81.
2. *Personal author(s) of books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974.
3. *Chapter in a book*
   Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

Tables

☐ Type each table double-spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give *each* column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. (In footnotes, define all abbreviations that are used in each table.) For footnotes, use lower-case italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

☐ Cite each table in the text in consecutive order.

☐ If data are used from another published (or unpublished) source, submit written permission from both author and publisher and acknowledge fully.

Illustrations

☐ Submit a complete set of figures with the original and each copy of the manuscript (4 sets total). Two sets must contain glossy illustrations, the other two sets may be high-quality photocopies. Figures must be in black and white and must be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.

☐ Send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm, instead of original drawings, roentgenograms, or other material.

☐ Many computer-generated figures are unsatisfactory for reproduction and should be professionally redrawn. Lettering should be of adequate size to retain clarity after reduction (*final* lettering size in print should be 1.5 mm high). Symbols, cross-hatching, and stippling within a figure should be sharp and distinct enough to retain uniqueness after reduction.

☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures. Do not mount them on cardboard or scratch them by using paper clips. Do not bend figures.

☐ Photomicrographs must have internal scale markers. Symbols, arrows, and letters used in the photomicrographs should contrast with the background.

☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from both the author and the publisher to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

☐ If a human subject is identifiable in the illustration, written consent must be obtained from the patient or legal guardian.

Legends for Illustrations

☐ Type legends for illustrations double-spaced starting on a separate page, with arabic numerals corresponding to the illustrations.

☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

☐ Define all abbreviations used in each illustration.

Abbreviations

☐ **At first mention of terminology in text, spell out in full and follow immediately with the abbreviation (enclosed within parentheses).**

☐ **Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.**

☐ **Consult the following sources for abbreviations:**

1. **CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 5th ed. Bethesda, Maryland: Council of Biology Editors, 1983;**
2. **American Medical Association. Manual of style. 8th ed. Baltimore, Maryland: Williams & Wilkins, 1989.**

Exclusive Publication Statement

☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a cover letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.

☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

Classified Advertising

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701E/L

The Department of Anesthesiology at the University of Texas Medical School in Houston is recruiting faculty at assistant professor, associate professor, and professor levels. Applicants must be board certified or board eligible and able to obtain a Texas medical license. The faculty positions include responsibilities for teaching, supervising and providing patient care, and participation in clinical or laboratory research and administrative functions of the department. The department has significant and expanding responsibilities in the areas of pain management, obstetrical anesthesia, neuroanesthesia, cardiac and vascular anesthesia, and hyperbaric medicine. Interested individuals should send a copy of curriculum vitae and names, addresses, phone numbers, and permission to contact three reference sources. Information should be sent to Jeffrey Katz, MD, Chairman, Department of Anesthesiology, University of Texas Medical School, 6431 Fannin, Houston, TX 77030. The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

873C/H

ILLINOIS: ANESTHESIOLOGIST
To join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approximately 40,000 (35-mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 887D/L.

887D/L

EASTERN PENNSYLVANIA
Hospital needs two board-certified/board-eligible anesthesiologists to join a fee-for-service group in a 225-bed progressive hospital. Applicants must be a PGIV preferrably with pain management, residency rotation. Reply to Box 888D/I.

888D/I

UPSTATE NEW YORK
Hudson River Valley—Columbia-Greene Medical Center is recruiting four fee-for-service anesthesiologists including a chief. Financial guarantee. C-GMC is located 80 miles north of NYC and 30 miles south of Albany. No neuro, open heart, or sick neonates. Staff and administration are supportive. Clear opportunity for growth. Office support available. Send CV and date of availability to Susan Bane, MD, Medical Director, C-GMC, 71 Prospect Avenue, Hudson, NY 12534.

893D/G

TENNESSEE
Expanding department requires additional anesthesiologists. Full-time positions available at levels of instructor to associate professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) meet Tennessee license requirements. (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curriculum vitae, bibliography, and the names and addresses of three references to Roger S. Cicala, MD, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

894E/G

---

6 MONTHS PER YEAR
Need well-trained anesthesiologist partner for flexible 6 months per year. Regional Medical Center. Interest and ability in basic pain management, ICU, OB, and OR anesthesia required. Financial package $100,000–$125,000. Michael Boyer, MD, 2 Clark Bass Boulevard, Suite 104, McAlester, OK 74501, (918) 426-5516.

895E/G

FLORIDA
BE/BC anesthesiologist needed to join busy group practice, serving a fast-growing 130-bed community hospital. Beautiful small Gulfcoast community, no neuro or OH. Send CV to Gulfcoast Anesthesia Specialists, 6630 West Gulf to Lake Highway, Crystal River, FL 32629.

904F/H

THE UNIVERSITY OF CALIFORNIA DAVIS
School of Medicine is recruiting for the position of Chair for the Department of Anesthesiology. The appointment will be made at the associate professor/professor level. Candidates must have an MD degree, be board certified in anesthesiology, eligible for licensure in California, and have a strong background in administration, teaching, and research. Please forward a curriculum vitae, a letter outlining background and experience, and the names and addresses of five professional references to Herbert Berkoff, MD, Chairman, Anesthesiology Chairmanship Search Committee, 4301 X Street, Sacramento, CA 95817. This position will remain open until filled. However, applications cannot be accepted after October 1, 1992. The University of Califor-

---

CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

nia is an Equal Opportunity/Affirmative Action Employer.

906FG

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY

The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conference, and teaching responsibilities are part of the fellowship experience. Interested individuals should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 83131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

912F/L

PEDIATRIC ANESTHESIOLOGIST

BC/BE to join a private group in growing Pediatric Medical Center in Atlanta, Georgia. No open hearts or transplants. Send CV to Box 916F/H.

916F/H

PAIN FELLOWSHIP, DIVISION OF PAIN MANAGEMENT, DEPARTMENT OF ANESTHESIOLOGY, SUNY HEALTH SCIENCE CENTER AT SYRACUSE

One or two competitive CA-4 positions available. Extensive clinical exposure to acute and chronic pain management, including cancer and pediatric patients. Opportunity for clinical and laboratory research relative to pain management availabe. Please send curriculum vitae to P. Sebastian Thomas, MD, Director, Pain Treatment Service, SUNY Health Science Center, Syracuse, NY 13210. Equal Opportunity Employer.

917F/H

PEDIATRIC ANESTHESIOLOGIST

The Section of Pediatric Anesthesiology at Arkansas Children's Hospital is seeking an additional faculty member. Candidates should be BC/BE with an approved fellowship in pediatric anesthesiology. Arkansas Children's Hospital is a state-of-the-art facility providing tertiary and primary care to children in six surrounding states. More than 6000 surgical procedures are performed each year. All facets of care are provided including an active acute and chronic pain service. Interested candidates should apply to Raeford E. Brown, Jr, MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

919F/H

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology and Critical Care Medicine has immediate faculty positions at the Instructor, Assistant Professor, Associate Professor, and Professor levels for candidates with experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia and critical care medicine. Responsibilities include the teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interests will be provided. It is expected that candidates who apply for CCM positions will have or be eligible for subspecialty certification. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 87131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

913F/L

OB Anesthesiologist sought for large university-affiliated hospital. Approximate 300 deliveries a month with many high risk. In-house neonatologists. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S. H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564.

872CEGIK

ANESTHESIOLOGIST

BC/BE. Openings to join group at 500-bed hospital plus busy outpatient center in Erie, Pa. All types of anesthesia including pain management. Beautiful area with year-round recreation. Competitive salary with opportunity for partnership. Send CV to Anesthesia Consultants of Erie, 225 West 25 Street, Suite 408, Erie, PA 16502.

922GH

Immediate opening for a BC/BE anesthesiologist to join six MD anesthesiologists in a fee-for-service practice in a 350-bed hospital in a retirement community in Sun City, Arizona. No OB, open heart, trauma, or pediatrics. Send replies to Box 923GH.

923GH

Texas Tech University Health Sciences Center, Lubbock has faculty positions available for board certified/eligible anesthesiologists with training/experience in subspecialty activities (cardiac anesthesia, critical care, and obstetric). The Department has a tradition of strong support to research activities. Salary is competitive with good benefits. Lubbock is located in the sunbelt within driving distance of the mountains and skiing. It is the home of a major university offering an excellent lifestyle. Equal Opportunity Employer. Please address correspondence, with references and curriculum vitae, to Gabor B. Racz, MD, Chairman, Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

924GH

ANESTHESIOLOGY RESEARCH FELLOWSHIPS

The University of Iowa Department of Anesthesia offers NIH-supported experiences (1–3 years in length) in both laboratory and clinical research for anesthesiologists. This program is designed to provide an important interval of minimal clinical responsibility so as to allow preparation for a career in academic practice. Areas of research interest for which mentorship is offered include mechanisms of anesthesia and pain; cardiovascular physiology and pharmacology; neurosciences in anesthesia; maternal/fetal physiology and pharmacology; pediatric anesthesiology; and cognitive psychopharmacology. In addition, multidisciplinary collaboration within the College of Medicine provides excellent opportunities for integration of methodologic and theoretical advances into this training experience. The University of Iowa is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply. Please direct inquiries to John H. Tinker, MD, Professor and Head, Department of Anesthesia, University of Iowa, Iowa City, IA 52242.

925G

NORTH EAST, INDIANA

Group seeking BC/BE anesthesiologists to join large MD-only group. All types of anesthesia provided, including OH and OB. Immediate opening. Early partnership offered. Send CV to Box 926G/I.

926G/I

The Department of Anesthesiology at Duke University Medical Center invites qualified full-time faculty to apply for positions in the following categories: NEUROANESTHESIA—We are seeking an academic faculty candidate trained in neurosurgical anesthesia to lead a developing neuroanesthesia section as chief of the section. This opportunity requires a candidate with a primary interest in investigative research and teaching in addition to clinical expertise in all aspects of neuroanesthesiology including an interest in the development of a neurological intensive care unit. A new spacious neuroscience facility at Duke fosters interdisciplinary relationships with

neuropharmacology, neuroradiology, neurobiology, and neurology. The neuroscience program at Duke University is one of the five developing centers of excellence at this nationally prominent university. CRITICAL CARE MEDICINE—We are seeking individuals who are ABA certified or board eligible in critical care medicine, for the position of Co-Director, SICU at the Durham VA Medical Center (where a new ICU tower is under construction) and/or as critical care faculty in the SICU at Duke University Medical Center. Faculty will play an essential role in the coordination of care in a multidisciplinary consulting service and in the development of an interdisciplinary Critical Care Fellowship program. GENERAL INTERESTS AND CLINICAL PHARMACOLOGY—We have positions for starting academicians whose subspecialty interests are broad or undefined, but who desire to begin an academic career in a setting with an emphasis on clinical research in pharmacology and epidemiology as it relates to the practice of anesthesiology.

Academic titles and compensation for the above positions will be commensurate with experience and credentials in education, clinical service, and research. Candidates must be board certified or board eligible, and eligible for an unrestricted North Carolina medical license. Please send letter of application and curriculum vitae to J. G. Reves, MD, Box 3094, Duke University Medical Center, Durham, NC 27710. Duke University is an Affirmative Action-Equal Opportunity Employer.

927G/I

ANESTHESIOLOGIST
Research Associate position available at 1200-bed VA Medical Center for BC anesthesiologist. Prior fellowship training in cardiac anesthesia required. Forward CV to Shukri F. Khuri, MD, Chief of Surgery, Brockton/West Roxbury VA Medical Center, 1400 VFW Parkway, West Roxbury, MA 02132. An Equal Opportunity Employer.

928G

LAKE CHAMPLAIN-ADIRONDACK REGION NEW YORK
Growing group seeks a BC/BE anesthesiologist at 410-bed regional referral hospital. Department consists of six anesthesiologists and two CRNAs for 6000 cases/year. No hearts or transplants. Mostly Narkomed 3 machines with H-P Merlin monitors. Plattsburgh is located at the foothills of the Adirondacks and on Lake Champlain, the sixth largest lake in the country. Montreal and Lake Placid region are within 1-hour drive. Excellent public and private schools, state university, affordable real estate, active arts council, and wide variety of recreational activities combine to offer an extraordinary family environment. For details or to view a video of the hospital and community, contact Hannah Hanford, Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

929G/I

CALIFORNIA
University of California, Irvine: Openings for faculty positions in the Department of Anesthesiology. (1) Assistant or associate professor level in the in-residence series. Responsibilities include teaching and research. (2) Clinical instructor and assistant professor level in the clinical series. Responsibilities include teaching and clinical service. Participation in research is highly desirable but not mandatory

Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUSIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT
Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

CAN'T GET AWAY? PHONEPREP IS AS CONVENIENT AS YOUR TELEPHONE
Take mock orals and learn oral test-taking techniques by PHONE — from the originator of telephone mock orals and tutorials in anesthesiology. (419) 843-4480.

908G

DON'T PROCRASTINATE
Prepare early for the ITE/written boards. Unique study program with practice questions and answers with explanations, guessing techniques, Keywords 1991, and much more. Call the original MEDTEXT: 1-800-695-6301; 24 hours. MC/V accepted.

757I/G

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS
The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/H

Dial 1-800/RENT-A-DOC
For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-800/736-8236 * PO Box 640 * Michigan City, IN 46360.

832A/L

J. STEPHENS MAYHUGH AND ASSOCIATES, INC. LOCUM TENENS ANESTHESIA SERVICES
Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

755I/H

A WEEKEND OF MOCK ORAL EXAMS
Mock orals, not lectures. We are the original course in this format. 20 hours category I CME credit, two board-certified instructors, 12 students maximum. Tampa, July 31–August 2; Dallas, August 21–23. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

896E/G

DANIEL & YEAGER LOCUM TENENS
Daniel & Yeager is the only name you need for locum tenens. Anesthesia is our specialty, so you are assured of our personal attention. Earn a premium income while eliminating administrative headaches and malpractice premiums; we cover it all. Call 1-800-264-1919 or write to 200 Clinton Avenue, NW, Suite 400, Huntsville, AL 35801.

898E/L

INTRODUCING . . . "BOARD CARDS"
A unique study system, designed specifically for the oral boards. Study cards are formatted to provide a well-organized, systematic approach, using the latest references. Over 300 cards in 20 subject categories, $245 postpaid (MC/VI). For more information write or call: BOARD CARDS, P.O. Box 577, Shasta, CA 96087, (800) 638-1294.

914FG

INDEX TO ADVERTISERS

Augustine Medical
Bair Hugger A10

Burroughs Wellcome Company
Mivacron ..... A37 thru A45
Nuromax ..... A17 thru A20
Tracrium A4, A5, A6

Janssen Pharmaceuticals
Alfenta ..... Cover 3 & Cover 4

Marion Merrell Dow
Cardizem Injectable ..... A21 thru A24

Massachusetts General Hospital
Employment Opportunity A6

Mercury Medical
2001 Laryngoscope Blade A46

Organon Pharmaceuticals
Arduan ..... Cover 2 & A1
Norcuron A32, A33, A34

Osler Institute
Course A14

Peripheral Systems Group
Smart Needle A2, A3

Preferred Physicians Mutual A12

Hoffman La Roche
Mazicon ..... A25 thru A30
Versed A35, A36

University of California, San Francisco
Employment Opportunity A31

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society



Editorials

Pressure Support Ventilation During Spontaneous Ventilation

Convulsions and Pediatric Regional Anesthesia

Original Articles

Pressure Support Ventilation

Esmolol vs Nitroprusside for Controlled Hypotension

Hypotensive Anesthesia With Nicardipine

Hypocarbia and Sufentanil Dynamics

Pipecuronium and Volatile Anesthetics

Volatile Anesthetics and Endothelium-Dependent Relaxation Factor

Ketorolac and Biliary Tract Pressure

Ambulatory Anesthesia

Ketorolac vs Bupivacaine and Postoperative Arthroscopy Pain

Cardiovascular Anesthesia

Echocardiographic and CABG Surgery

Endobronchial Insufflation of O_2

Neurosurgical Anesthesia

New Catheter for Air Retrieval From Venous Air Embolism

Intracranial Pressure and Dexmedetomidine

Methylprednisolone, Eicosanoid, and Head Trauma

Obstetric Anesthesia

Epidural PCA for Cesarean Delivery

Pediatric Anesthesia

Alfentanil-Induced Rigidity in Newborn Infants

Telephone Questionnaire for Preoperative Screening

Regional Anesthesia and Pain Management

Oral Clonidine and Spinal Anesthesia

Continuous 3-in-1 Nerve Block Infusion for Postoperative Analgesia

Interpleural Bupivacaine of 0.25% vs 0.5%

Review Article

Compartment Syndromes

ISSN 0003-2999 Volume 75, Number 2, August 1992

Now available in 20 mg/20 mL vials

THE LOGICAL CHOICE



CRUCIAL PARAMETERS IN SELECTING A NEUROMUSCULAR BLOCKING AGENT

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY		
To 25% of control	25-40 min[3]	35-45 min[5]
To 95% of control	45-65 min[3]	60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

* Dose of atracurium above 0.5 mg/kg is not recommended.
† As originally supplied by the respective manufacturers.
‡ Storage after reconstitution varies with solution. See package insert.

Norcuron®
(vecuronium bromide) for injection



THE LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon
ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for nonelective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to limited recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04–0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25–30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25–30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45–65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04–0.06 mg/kg with inhalation anesthesia and 0.05–0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effect, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80–100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20–40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25–60 percent, 45–60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug μg/kg/min	Patient Weight – kg						
	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution — Sterile water for injection — Lactated Ringers
5% glucose in water — 5% glucose in saline

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED:

10 mL vials (10 mg vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP). 22 g 1¼" needle. Boxes of 10 NDC No. 0052-0441-60

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP). Boxes of 10 NDC No. 0052-0441-17

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-0441-15

20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-0442-46

STORAGE: 15°–30°C (59°–86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription. REVISED 1/

References

1. Gallo JA, Cork RC, Puchi P. Comparison of effects of atracurium and vecuronium in cardiac surgical patients. *Anesth Analg* 1988;67:161-165. 2. Basta SJ, Savarese JJ, Ali HH, et al. Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiol.* 1983;58(3):A273. 3. Norcuron® (vecuronium bromide) for injection package insert. 4. Kaufman JA, Dubois MY, Chen JC, Lea D. Pharmacodynamic effects of vecuronium: A dose response study. *J Clin Anesth.* 1989;1(6):434-439.5. Tracrium® injection (atracurium besylate) package insert. 6. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth.* 1985;57:550-553.

*Tracrium is a registered trademark of Burroughs Wellcome Co.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

©1992 ORGANON INC. ORG-13842 PRINTED IN USA FEBRUARY 199

ANESTHESIA & ANALGESIA

Official Journal of the International Anesthesia Research Society

Editor-in-Chief
Ronald D. Miller
San Francisco, California

Associate Editor-in-Chief
John H. Tinker
Iowa City, Iowa

EDITORIAL BOARD

David R. Bevan
Vancouver, British Columbia, Canada

Thomas J. Gal
Charlottesville, Virginia

Kenjiro Mori
Kyoto, Japan

Walter S. Nimmo
Edinburgh, Scotland

Nathan L. Pace
Salt Lake City, Utah

Richard J. Palahniuk
Minneapolis, Minnesota

Michael F. Roizen
Chicago, Illinois

John J. Savarese
New York, New York

Hugo Van Aken
Leuven, Belgium

Section Editors

Ambulatory Anesthesia
Patricia A. Kapur
Los Angeles, California

Cardiovascular Anesthesia
Joseph G. Reves
Durham, North Carolina

Critical Care and Trauma
Ronald G. Pearl
Stanford, California

Neurosurgical Anesthesia
Donald S. Prough
Galveston, Texas

Obstetric Anesthesia
Mieczyslaw Finster
New York, New York

Pediatric Anesthesia
Paul R. Hickey
Boston, Massachusetts

Regional Anesthesia and Pain Management
Phillip O. Bridenbaugh
Cincinnati, Ohio

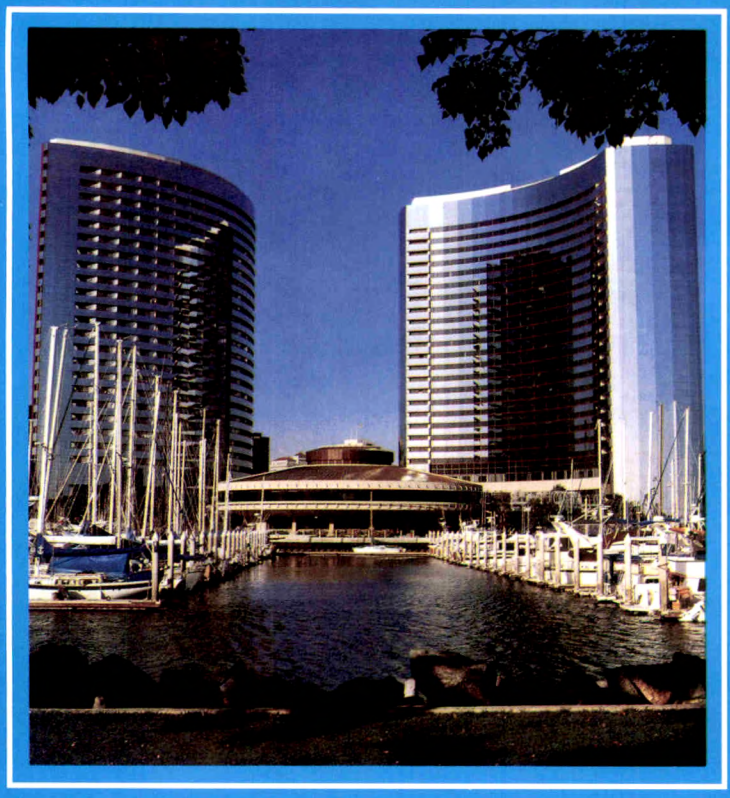
Book Reviews
Norig Ellison
Philadelphia, Pennsylvania

Managing Editor
King C. Kryger

Editorial Assistant
Christine A. Arturo

Manuscripts and editorial correspondence should be addressed to: King Kryger, PhD, Managing Editor, *Anesthesia & Analgesia*, 3497 Sacramento Street, San Francisco, CA 94118 [telephone: (415) 292-7964; FAX: (415) 292-5157]. For information concerning preparation of manuscripts, see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to Norig Ellison, MD, Book Review Editor, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.



IARS 67th CONGRESS

MARCH 19 -23, 1993

San Diego Marriott Hotel & Marina

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

CALL FOR PAPERS

If you have an abstract that you would like to have considered for inclusion on the scientific program (either oral or poster presentation), please complete and return the adjacent form. Abstract submission forms will be forwarded in May, 1992 to those requesting them. Scientific exhibit applications are also available. The deadline date for submission of abstracts is July 31, 1992. There is no absolute deadline for scientific exhibit submissions.

IARS
2 Summit Park Drive, #140
Cleveland, Ohio 44131
Fax #: (216) 642-1127
Phone #: (216) 642-1124

Re: 67th Congress, March 19-23,1993
San Diego Marriott Hotel & Marin
San Diego, California

Please send me
(_____) Abstract submission forms for paper/poster presentations
(_____) Scientific exhibit applications

Name_____

Address_____

_____

_____

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

Contents

Volume 75, Number 2, August 1992

EDITORIALS

161 **Pressure Support Ventilation: Technology Transfer From the Intensive Care Unit to the Operating Room**
Ronald G. Pearl and Myer H. Rosenthal

164 **Convulsions Associated With Pediatric Regional Anesthesia**
Charles B. Berde

ORIGINAL ARTICLES

167 **Pressure Support Ventilation Decreases Inspiratory Work of Breathing During General Anesthesia and Spontaneous Ventilation**
Joan M. Christie and Robert A. Smith

172 **Esmolol Is More Effective Than Sodium Nitroprusside in Reducing Blood Loss During Orthognathic Surgery**
William S. Blau, Enid R. Kafer, and Jay A. Anderson

179 **Long-Term Hypotensive Technique With Nicardipine and Nitroprusside During Isoflurane Anesthesia for Spinal Surgery**
Jean-Marc Bernard, Norbert Passuti, and Michel Pinaud

186 **Effects of Hypocarbia on the Pharmacodynamics of Sufentanil in Humans**
Richard S. Matteo, Eugene Ornstein, Arthur E. Schwartz, William L. Young, Jeffrey Weinstein, and Charles F. Cain

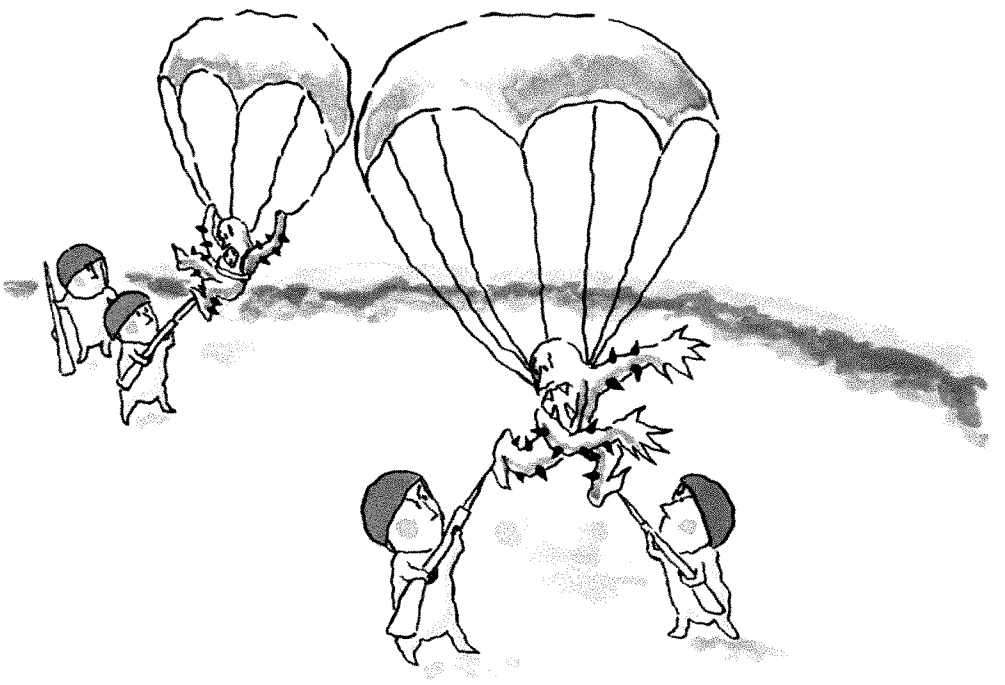
193 **Pipecuronium-Induced Neuromuscular Blockade During Nitrous Oxide-Fentanyl, Enflurane, Isoflurane, and Halothane Anesthesia in Surgical Patients**
Mohamed Naguib, Mohamed Seraj, and Essam Abdulrazik

198 **Halothane and Isoflurane Inhibit Endothelium-Dependent Relaxation Elicited by Acetylcholine**
Hiroshi Toda, Kumi Nakamura, Yoshio Hatano, Makoto Nishiwada, Masahiro Kakuyama, and Kenjiro Mori

204 **Effects on Biliary Tract Pressure in Humans of Intravenous Ketorolac Tromethamine Compared With Morphine and Placebo**
H. Krimmer, R. E. S. Bullingham, J. Lloyd, and H. P. Bruch

Anesthesia & Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. *© 1992 by the International Anesthesia Research Society.* *Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1992 applying to IARS members: USA and possessions, $95.00 per year; in all other countries, $120.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1992 applying to non-IARS members: Institutions, $150.00; nonmember individuals, $110.00. Outside the USA and possessions, please add $35.00 for surface postage and handling. For airmail, add $80.00 in USA, Canada, and Mexico; $70.00 for surface airlift to Europe; $85.00 for surface airlift to Japan; and $160.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia & Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.*

Cold Increases Infection Risk



Wound infection is the largest single complication of surgery and is more costly than all anesthesia complications combined. Even mild hypothermia decreases the migration of polymorphonucleocytes (PMNs) to infection sites and impairs cell mediated immunity. Mild hypothermia at the time of bacterial challenge has been shown to suppress the immune response and increase the size of infections. Bair Hugger® Warming Therapy maintains patient normothermia during surgery and arms the immune system at the time of bacterial challenge. In a warm patient, invading bacteria will have less opportunity to colonize, and defenders can more easily eliminate them. Your patients deserve a fighting chance. Bair Hugger® Warming Therapy. From Augustine Medical, Inc.

AUGUSTINE MEDICAL, INC.
Practical Solutions to Common Problems in Acute Care™
10393 West 70th Street, Eden Prairie, Minnesota 55344
(612) 941-8866 • (800) 733-7775 • Fax: (612) 941-8858

Bair Hugger

AMBULATORY ANESTHESIA

208 **Effects of Ketorolac and Bupivacaine on Recovery After Outpatient Arthroscopy**
Ian Smith, Robert A. Shively, and Paul F. White

CARDIOVASCULAR ANESTHESIA

213 **Echocardiographic Analysis of Dysfunctional and Normal Myocardial Segments Before and Immediately After Coronary Artery Bypass Graft Surgery**
Paolo Voci, Federico Bilotta, Solomon Aronson, Giovanni Scibilia, Quintilio Caretta, Corrado Mercanti, Benedetto Marino, Ronald Thisted, Michael F. Roizen, and Attilio Reale

219 **Continuous Endobronchial Insufflation During Internal Mammary Artery Harvest**
Robert J. N. Watson, Richard Szarko, Colin F. Mackenzie, Alejandro J. Sequeira, and George M. Barnas

NEUROSURGICAL ANESTHESIA

226 **Modification of a New Catheter for Air Retrieval and Resuscitation From Lethal Venous Air Embolism: Effect of Nitrous Oxide on Air Retrieval**
Alan A. Artru

232 **Intracranial Pressure Effects of Dexmedetomidine in Rabbits**
Mark H. Zornow, Mark S. Scheller, Patrick B. Sheehan, Martin A. P. Strnat, and Mishiya Matsumoto

238 **Methylprednisolone Does Not Decrease Eicosanoid Concentrations or Edema in Brain Tissue or Improve Neurologic Outcome After Head Trauma in Rats**
Yoram Shapira, Alan A. Artru, Gal Yadid, and Ester Shohami

OBSTETRIC ANESTHESIA

245 **Epidural Patient-Controlled Analgesia: An Alternative to Intravenous Patient-Controlled Analgesia for Pain Relief After Cesarean Delivery**
Robert K. Parker and Paul F. White

PEDIATRIC ANESTHESIA

252 **Alfentanil-Induced Rigidity in Newborn Infants**
Marja-Leena Pokela, Pauli T. Ryhänen, Maila E. Koivisto, Klaus T. Olkkola, and Anna-Liisa Saukkonen

258 **Preoperative Screening for Pediatric Ambulatory Surgery: Evaluation of a Telephone Questionnaire Method**
Ramesh I. Patel and Raafat S. Hannallah

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

262 **Prolongation of Tetracaine Spinal Anesthesia by Oral Clonidine**
Kouichi Ota, Akiyoshi Namiki, Yoshihito Ujike, and Ikuko Takahashi

265 **Continuous Low-Dose 3-in-1 Nerve Blockade for Postoperative Pain Relief After Total Knee Replacement**
Neal D. Edwards and Eluned M. Wright

268 **Continuous Interpleural Infusion of Bupivacaine for Postoperative Analgesia After Surgery With Flank Incisions: A Double-Blind Comparison of 0.25% and 0.5% Solutions**
Jack W. van Kleef, E. Angelique Logeman, Anton G. L. Burm, Jan Willem H. de Voogt, René A. G. Mooren, and Irene M. van Kleef-Mannot

REVIEW ARTICLE

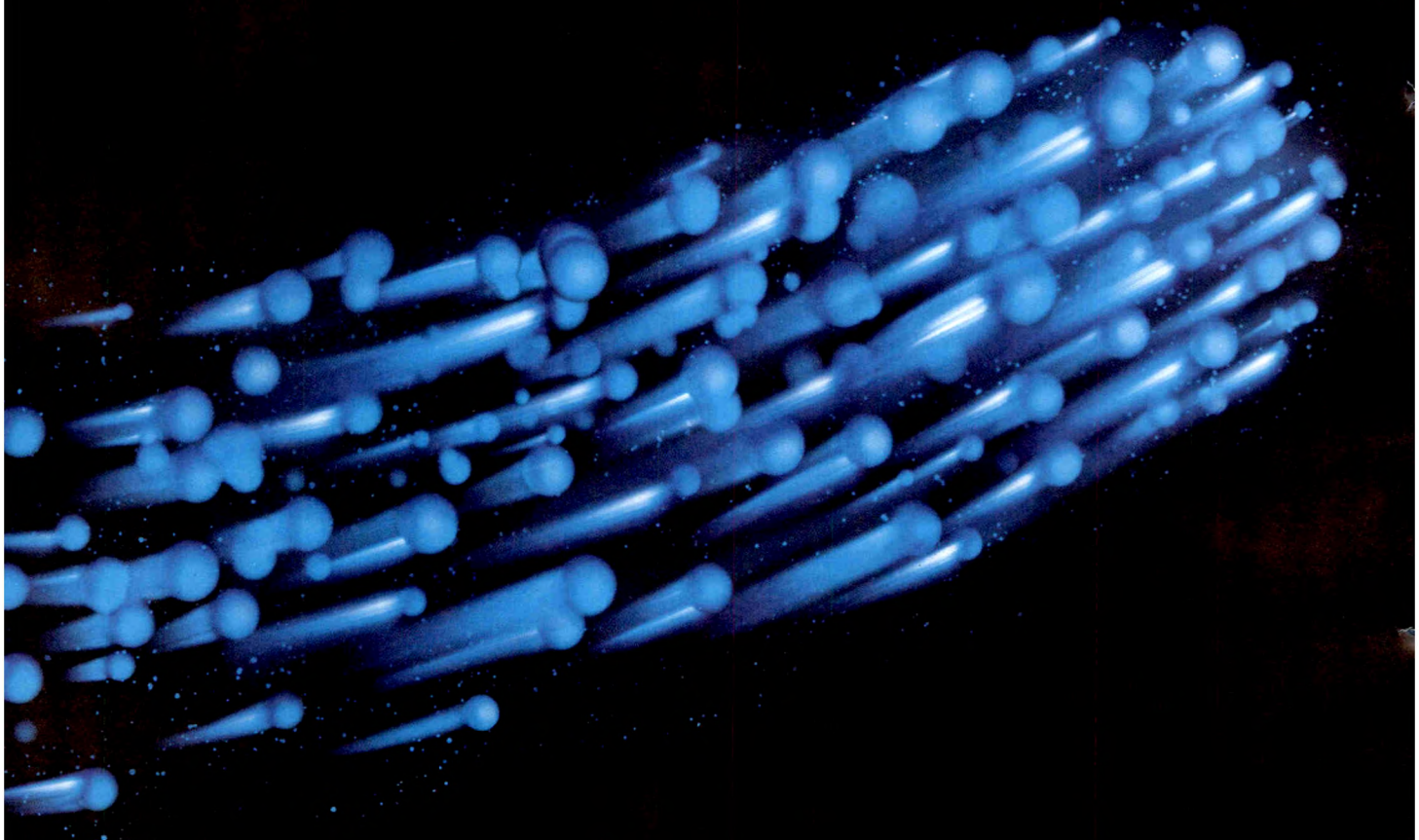
275 **Compartment Syndromes: Concepts and Perspectives for the Anesthesiologist**
John T. Martin

CASE REPORTS

284 **Seizures Occurring in Pediatric Patients Receiving Continuous Infusion of Bupivacaine**
Rita Agarwal, David P. Gutlove, and Charles H. Lockhart

287 **Bupivacaine Toxicity Secondary to Continuous Caudal Epidural Infusion in Children**
John J. McCloskey, Steven E. Haun, and Jayant K. Deshpande

new Suprane™ desflurane



Coming soon from

Anaquest

A BOC Health Care Company
Critical Care Worldwide

© 1992 Anaquest Inc

CASE REPORTS—*continued*

291 **Succinylcholine-Induced Hyperkalemic Arrest in a Patient With Severe Metabolic Acidosis and Exsanguinating Hemorrhage**
David E. Schwartz, Brian Kelly, James E. Caldwell, A. Sue Carlisle, and Neal H. Cohen

294 **Succinylcholine-Induced Hyperkalemia 8 Weeks After a Brief Paraplegic Episode**
James W. Greenawalt III

296 **Vertebral Artery Pseudoaneurysm: A Rare Complication of Internal Jugular Vein Catheterization**
Hiroshi Aoki, Toshiki Mizobe, Shinnji Nozuchi, Tetsuo Hatanaka, and Yoshifumi Tanaka

299 **Craniotomy in a Patient With Eisenmenger's Syndrome**
Mark A. Chaney

LETTERS TO THE EDITOR

303 **A "New" Needle?**
J. Antonio Aldrete and A. Torrieri

303 ***In Response***
Joseph Eldor

304 **A Simple Method of MDI Administration in the Intubated Patient**
Edwin Dunteman and George Despotis

305 **Reliability of the Slope of the End-Systolic Pressure-Volume Relationship as Individual Index of Myocardial Inotropic State**
Stefan G. De Hert and Karel M. Vermeyen

305 **Use of a Wilson Convex Frame in Removing "Irretrievable" Epidural Catheters**
Robert J. Start, Daniel J. Greenberg, and Norman L. Herman

306 **Labeling of Syringes to Prevent "Drug Swaps"**
Terry W. Latson

307 **A Simple Device to Demonstrate the Law of Laplace**
Rafael Ortega

307 **The 3.5/4.5 Modification for Fiberscope-Guided Tracheal Intubation Using the Laryngeal Mask Airway**
Graham D. Chadd, Andrew J. Walford, and David L. Crane

308 **Effect of Propofol in Brainstem Auditory Evoked Responses**
R. V. Reddy, S. S. Moorthy, S. F. Dierdorf, R. D. Yee, and Linda Link

309 **When Is a Fact, in Fact, a Fact?**
J. Bruce Laubach

309 ***In Response***
Phillip E. Scuderi, Donald S. Prough, David L. Bowton, and Randy L. Anderson

309 **Plug It In!**
Shepard B. Stone

310 ***In Response***
William F. Eckhardt, Onofrio Patafio, and Francisco Cigarroa

310 **What Caused the Unilateral Epidurogram and Bilateral Epidural Analgesia?**
Fumio Asato and Fumio Goto

310 ***In Response***
Vito A. Peduto, Riccardo Tani, Luciana Marinelli, and Sergio Pani

311 **Reinserting a Catheter Into a Single-Use Adapter: An Unsafe Method**
Joseph Eldor

311 ***In Response***
Gary T. Kirchhoff

311 **Contralateral Anesthesia Following Interscalene Block**
Edward Gologorsky and Raymond F. Leanza

312 **Ventilatory Depression and Midazolam**
William W. Pond and Michael Hartman

312 ***In Response***
Christian M. Alexander, Lynn E. Teller, and Jeffrey B. Gross

313 **Interpleural Regional Analgesia—A Simple Cause of Catheter Obstruction**
Mohammad Maroof, Mahmood Siddique, and Rashid M. Khan

313 **Anesthetic Management in Charcot-Marie-Tooth Disease**
Joseph F. Antognini

313 ***In Response***
Robert S. Greenberg and Stephen D. Parker

PermaTail



THE PERMANENT MALPRACTICE PROTECTION PROGRAM
ONLY FOR SELECTED ANESTHESIOLOGISTS

PREFERRED
PHYSICIANS
MUTUAL
Risk Retention Group

204 Lucas Place
323 West 8th Street
Kansas City, Missouri 64105
Call Toll-free 800-562-5589

BOOK REVIEWS

314 **Drugs for the Heart by L. H. Opie, ed.**
R. K. Baumgarten

314 **New Developments in Pediatric Anesthesia. Volume 9, No. 4 of Anesthesia Clinics of North America by Jerrold Lerman, ed.**
Philippa Newfield

315 **A Glance at Transesophageal Echocardiography by R. A. Gal**
Martin D. Abel

315 **Dripps/Eckenhoff/Vandam Introduction to Anesthesia, 8th edition by D. E. Longnecker and F. L. Murphy, eds.**
Martin Helrich

316 **Books Received**

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

The **International Anesthesia Research Society** is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: David R. Bevan, MA, MB, BChir, Michael K. Cahalan, MD, Douglas B. Craig, MD, FRCPC, Bruce F. Cullen, MD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Joseph G. Reves, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: E. Paul Didier, MD, Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, and B. B. Sankey, MD.

Anesthesia & Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA.

© 1992 by the International Anesthesia Research Society.

Second class postage paid at New York, NY and at additional mailing offices.

Subscription information for 1992 applying to IARS members: USA and possessions, $95.00 per year; in all other countries, $120.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. Associate Membership is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). Educational Membership (at a reduced price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2-, 3-, or 4-year period upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, OH 44131-2553.

Subscription information for 1992 applying to non-IARS members: Institutions, $150.00; nonmember individuals, $110.00. Outside the USA and possessions, please add $35.00 for surface postage and handling. For airmail, add $80.00 in USA, Canada, and Mexico; $70.00 for surface airlift to Europe; $85.00 for surface airlift to Japan; and $160.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia & Analgesia*, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Single issues: Single copy information is available from Elsevier Science Publishing Co., Inc., upon request. Back volume (all issues prior to 1983) information is available from the IARS.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See Classified Ads section for submission of classified ad material.

All articles published in this journal become the property of the International Anesthesia Research Society. This journal has been registered with the **Copyright Clearance Center, Inc.** Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the center the per copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. The appropriate fee should be forwarded with a copy of the first page of the article to the Copyright Clearance Center, Inc., 27 Congress Street, Salem, MA 01970. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

All inquiries regarding copyrighted material from this publication, other than reproduction through the Copyright Clearance Center, should be directed to: Rights and Permissions Department, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. FAX 212-633-3977.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) are processed through Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Prices are provided upon request.

This journal is abstracted/indexed in: Biological Abstracts, Chemical Abstracts, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Index Medicus, ISI/Biomed, and Science Citation Index.

On line text is available through **BRS Colleague**, 8000 Westpark Drive, McLean, VA 22102. Telephone: (800) 289-4277.

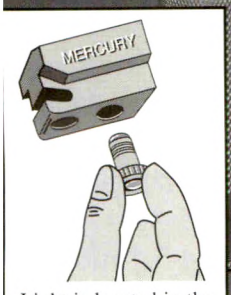
This journal is printed on acid-free paper.

Put a MERCURY® Fiberoptic Blade



On Your Handle*





Light is located in the bottom of the blade. Easy access makes replacement simple.

The MERCURY® 2001 FIBERLIGHT® Laryngoscope Blade saves you money yet gives 400% more light, virtually eliminates flickering and fits most standard handles.*

* Standard laryngoscope handles with fittings manufactured to ISO 7376 standards.

Call or write today for a copy of our Laryngoscope Catalog

MERCURY® MEDICAL
11300 A - 49th Street North
Clearwater, FL 34622-4800
(813) 573-0088 • 1-800-237-6418
FAX (813) 573-6040

CLIP AND RETURN FOR INFORMATION

NAME _____

TITLE _____

HOSPITAL/FIRM _____

ADDRESS _____

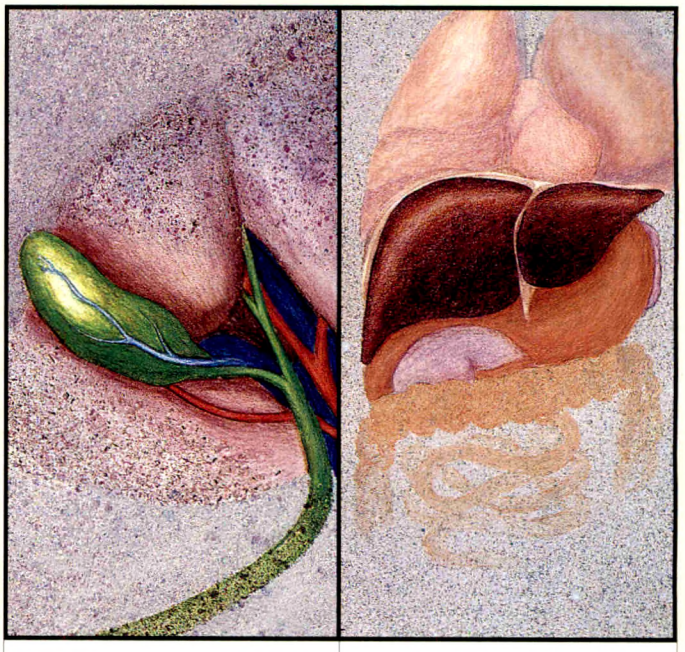
CITY _____ STATE _____ ZIP _____

PHONE _____

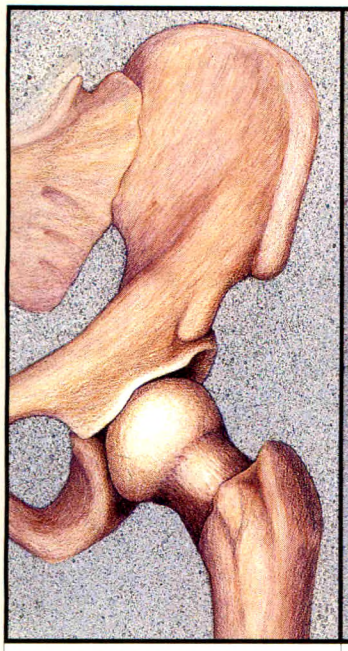
Tracrium®

For many procedures

For many reasons



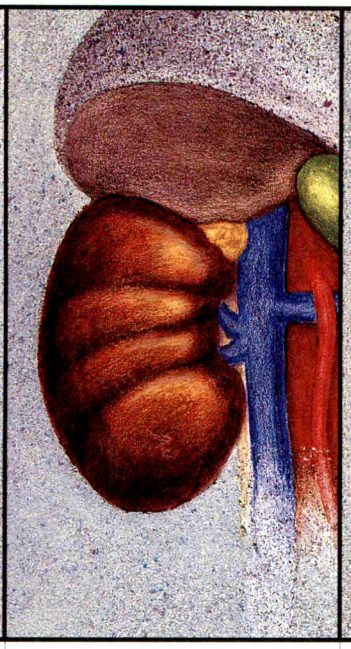
Cholecystectomy	Biliary tract repair
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]



Total hip replacement

Common patient type
Elderly women and men

Advantage of Tracrium
Recovery time unaffected by age.[3]



Renal surgery

Common patient type
Both adults and children

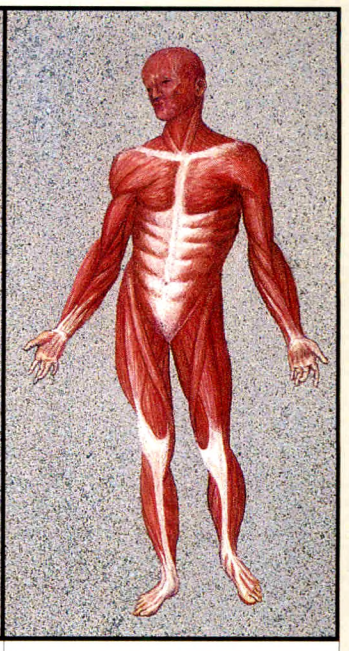
Advantage of Tracrium
Recovery time unaffected by renal dysfunction.[2]



Neurosurgery for trauma

Common patient type
Both adults and children

Advantage of Tracrium
Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]



Everyday procedures

Common patient type
Average

Advantage of Tracrium
The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM® *INJECTION*
(atracurium besylate) 10 mg/mL

For predictable recovery

TR-Y03368

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67:1149-1153. 2. Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172. 3. d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology.* 1983;59:237-240. 4. Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology.* 1985;63:A331. Abstract. 5. Ebrahim Z, Bulkey H, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg.* 1988;67:S55. Abstract.

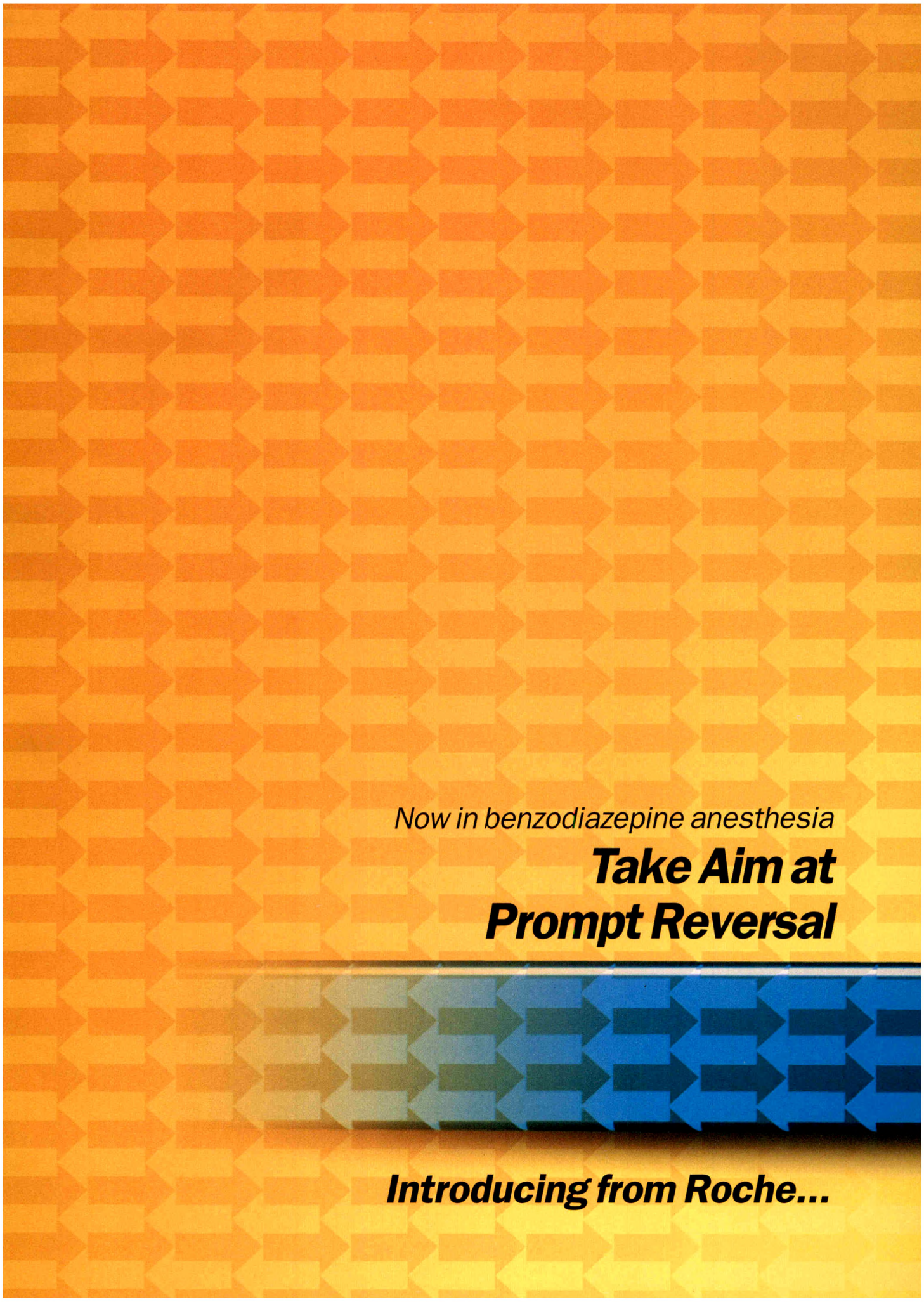
Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Copr. © 1991 Burroughs Wellcome Co. All rights reserved.

TR-Y03368

The **American Board of Anesthesiology (ABA)** will administer a written examination in **CRITICAL CARE MEDICINE** on Saturday, September 11, 1993. Diplomates of the ABA who apply and are judged to be qualified by virtue of their additional training will be accepted for examination. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1796. The deadline for receipt of completed applications in the Board office is March 1, 1993.

The **American Board of Anesthesiology (ABA)** will award a Certification of Added Qualifications in **PAIN MANAGEMENT** beginning in 1993. Diplomates of the ABA who apply for the certificate, and are judged to be qualified by virtue of their additional training or experience in Pain Management, will be accepted for the examination to be administered Saturday, September 11, 1993. An application may be requested by writing to the Secretary, American Board of Anesthesiology, 100 Constitution Plaza, Hartford, Connecticut 06103-1796. The deadline for receipt of completed applications in the Board office is March 1, 1993.


Now in benzodiazepine anesthesia
Take Aim at
Prompt Reversal
Introducing from Roche...

Awake and alert–effective reversal of sedation

- New MAZICON (flumazenil/Roche) rapidly and specifically reverses sedation produced by any benzodiazepine
- Promptly restores patients to consciousness—often within minutes of reaching an effective dose
- Reverses benzodiazepine sedative effects only—not the effects of narcotics or other CNS agents

Adverse effects

- The most common side effects in clinical trials were nausea and vomiting (11%), dizziness (10%), agitation (3-9%) and injection-site pain (3-9%)

Specific Reversal of Benzodiazepine Sedation

Seizures

- MAZICON is associated with seizures, most often in patients on benzodiazepines for long-term sedation or who are showing signs of serious cyclic antidepressant overdose. Practitioners should individualize the dosage and be prepared to manage seizures.

Worldwide experience

- Proven clinical experience in more than 50 countries

ROCHE®

Please see following pages for complete product information.

Copyright © 1992 by Hoffmann-La Roche Inc. All rights reserved.


1-800-756-7654
Call today for more information.
0.1 mg/mL
Mazicon I.V.
flumazenil/Roche
New
0.1 mg/mL
Mazicon I.V.
flumazenil/Roche
The reversal agent you've been waiting for
See important safety information about resedation.

Prompt Reversal of Benzodiazepine Sedation

Dosing and Administration

For reversal of benzodiazepine-induced general anesthesia or conscious sedation:

Initial dose: 0.2 mg *(2 mL) I.V. over 15 seconds*

➡ *If desired level of consciousness is not obtained after waiting an additional 45 seconds:*

Follow-up doses: 0.2 mg *(2 mL) I.V. every 60 seconds*

➡ *Up to a maximum dose of* ***1.0 mg*** *(10 mL)*

Management of resedation:

Repeat treatment above

Repeat treatment may be given no more often than every 20 minutes

➡ *No more than* ***1 mg*** *total dose should be given in any 5-minute interval*

➡ *No more than* ***3 mg*** *total dose should be given in any one hour*

Important safety information

➡ *Contraindicated in hypersensitivity to benzodiazepines or MAZICON; in patients taking benzodiazepines for control of potentially life-threatening conditions; and in patients showing signs of serious cyclic antidepressant overdose*

➡ *Patients should be monitored for resedation, respiratory depression or other residual effects of benzodiazepines*

➡ *MAZICON does not diminish the need for prompt detection of hypoventilation and the ability to intervene effectively by establishing an airway and assisting ventilation*

➡ *MAZICON should not be the initial treatment for benzodiazepine-induced hypoventilation; the first step is assisted ventilation*

➡ *In patients who are dependent on benzodiazepines, MAZICON may precipitate withdrawal syndromes*

Available in 5-mL and 10-mL vials



New

0.1 mg/mL

Mazicon I.V.™

flumazenil/Roche

The reversal agent you've been waiting for

See important safety information about resedation.

Roche Laboratories

ROCHE

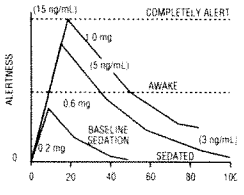
a division of Hoffmann-La Roche Inc.

MAZICON™
(flumazenil/Roche)

DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate.
Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



Minutes after Flumazenil Injection

*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{ss}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells.
Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng·hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.
The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg.
Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg.

Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness.
MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:
- in patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- in patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES. THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTI-DEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.

Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic anti-depressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely. Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependent on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.)
Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance

of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.

USE IN OVERDOSE: MAZICON is intended as an adjunct to, not as a substitute for proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.

Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.

HEAD INJURY: MAZICON should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.

USE WITH NEUROMUSCULAR BLOCKING AGENTS: MAZICON should not be used until the effects of neuromuscular blockade have been fully reversed.

USE IN PSYCHIATRIC PATIENTS: MAZICON has been reported to provoke panic attacks in patients with a history of panic disorder.

PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.

USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (see PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.

USE IN CARDIOVASCULAR DISEASE: MAZICON did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

USE IN LIVER DISEASE: The clearance of MAZICON is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction (see PHARMACOKINETICS). While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.

USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: MAZICON should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.

MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.

Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (5 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.

Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndrome for alcohol, barbiturates, and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when MAZICON was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.

Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.

USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)

Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of MAZICON is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)

INFORMATION FOR PATIENTS: MAZICON does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:

1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.

LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.

Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.

PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.

Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weaning was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.

LABOR AND DELIVERY: The use of MAZICON to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

MAZICON™ (flumazenil/Roche)

NURSING MOTHERS: Caution should be exercised when deciding to administer MAZICON to a nursing woman because it is not known whether flumazenil is excreted in human milk.

PEDIATRIC USE: MAZICON is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.

GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of MAZICON in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of MAZICON may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic anti-depressants) as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. MAZICON administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)

Two of the 448 patients who received MAZICON in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to MAZICON administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).

BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)

CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)

DIGESTIVE SYSTEM: Nausea and Vomiting (11%)

NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).

SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*Indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to MAZICON administration and/or reversal of benzodiazepine effects:

NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).

SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to MAZICON administration is unknown, but they are included as alerting information for the physician.

BODY AS A WHOLE: Rigors, shivering.

CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.

DIGESTIVE SYSTEM: Hiccup.

NERVOUS SYSTEM: Speech disorder (dysphoria, thick tongue).

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although MAZICON has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of MAZICON, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of MAZICON may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: MAZICON is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If MAZICON is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum stability, MAZICON should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.

REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)

In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)

MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of MAZICON. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)

Most patients with benzodiazepine overdose will respond to a cumulative dose of 1 to 3 mg of MAZICON, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded five minutes after receiving a cumulative dose of 5 mg MAZICON, the major cause of sedation is likely not to be due to benzodiazepines, and additional MAZICON is likely to have no effect. In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

SAFETY AND HANDLING: MAZICON is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Pressure Support Ventilation: Technology Transfer From the Intensive Care Unit to the Operating Room

Ronald G. Pearl, MD, and Myer H. Rosenthal, MD

Department of Anesthesia, Medicine, and Surgery, Stanford University Medical Center, Stanford, California

Mechanical ventilation has traditionally been used in two very different settings, namely, in the operating room for anesthetized patients with otherwise adequate respiratory function and in the intensive care unit (ICU) for patients with respiratory failure. An improved understanding of pulmonary pathophysiology and recent technological advances have significantly altered our current approach to mechanical ventilation in the ICU. The article in this issue of *Anesthesia & Analgesia* by Christie and Smith (1) on pressure support ventilation (PSV) for anesthetized patients is an attempt to define the value of these new approaches in the operating room setting.

Before the mid-1960s, volume-controlled ventilation in an assist/control mode was standard practice, and weaning from mechanical ventilation was primarily an all-or-none phenomenon with T-tube trials. Maintenance of functional residual capacity (FRC) was subsequently recognized as a major factor in allowing adequate oxygenation, decreased work of breathing (WOB), and prevention of atelectasis in the tracheally intubated patient. The use of positive end-expiratory pressure (PEEP) became increasingly popular as a means to maintain FRC and prevent atelectasis. In the early 1970s, intermittent mandatory ventilation was introduced to allow weaning from mechanical ventilation without the development of excessive WOB and resultant neuromuscular fatigue. Ventilatory support of the patient with acute respiratory failure primarily relied on large tidal volume breaths for alveolar ventilation and PEEP for maintenance of oxygenation and FRC.

The available intermittent mandatory ventilation circuits were often designed with demand valves requiring varying degrees of patient effort during spontaneous ventilation. Similar circuits became commonplace for the routine use of continuous positive airway pressure as a means of maintaining FRC in the presence of an endotracheal or tracheostomy tube. The value of maintaining FRC in reducing atelectasis, improving compliance, and reducing pulmonary vascular resistance was balanced by a potentially detrimental increase in WOB with use of such circuits. Although continuous-flow circuits as an alternative to demand valves were shown by Viale et al. (2) to reduce WOB, the majority of equipment available in the operating room and ICU used demand valve circuits.

The past decade has seen the development of multiple new ventilatory modes, such as high-frequency ventilation, high-frequency oscillation, airway pressure release ventilation, and inverse ratio ventilation. Each of these techniques improves oxygenation by maintaining a high mean airway pressure but prevents barotrauma by reducing peak airway pressure. These techniques are applicable primarily to the patient with poor pulmonary compliance and increased physiologic shunting caused by adult respiratory distress syndrome.

In contrast to these techniques that primarily address oxygenation, PSV is designed to maintain adequate alveolar ventilation without excessive WOB during spontaneous ventilation. Pressure support ventilation is used in two different ways. First, PSV may be used at low levels (5–10 cm H_2O) to decrease the increased WOB related to resistance of the endotracheal tube, work due to limited flow rates, and work due to demand valves (3). In this application, PSV results in an increased airway pressure during inspiration and reduces WOB to those values that would occur in the absence of exogenous factors.

A second application of PSV is its use as a method to increase alveolar ventilation and maintain adequate tidal volumes. Patients with respiratory failure frequently have decreased pulmonary (lung-thorax) compliance and increased minute ventilatory requirements, a combination that results in rapid, shallow breathing and markedly increased WOB. Pressure support ventilation may be used to decrease WOB to an acceptable level. During inspiration, the force

Accepted for publication April 15, 1992.

Address correspondence to Dr. Pearl, Department of Anesthesia, S268, Stanford University Medical Center, Stanford, CA 94305-5123.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

producing lung expansion is the difference between airway pressure and pleural pressure. By increasing airway pressure during inspiration, PSV increases this pressure differential, resulting in an augmented tidal volume without increased WOB. Because inspiration during PSV is terminated when air flow decreases below a set value, tidal volumes and minute ventilation are partially dependent on patient effort. In general, PSV is used at levels of 5–50 cm H_2O to increase tidal volume and decrease WOB.

Intensive care units were organized in the 1950s to provide optimal therapy for patients with respiratory failure, commonly as a result of poliomyelitis. Anesthesiologists became the principal caregivers, transferring knowledge and techniques accrued through decades of experience in the operating room. The use of large tidal volume (12–15 mL/kg) mechanical ventilatory support arose from studies demonstrating benefit in reducing atelectasis and maintaining FRC. In the majority of ICU units, the standard approach to mechanical ventilation of patients with normal lungs now includes intermittent mandatory ventilation with large (12–15 mL/kg) tidal volumes, low levels (approximately 5 cm H_2O) of PEEP, and low levels (5–8 cm H_2O) of pressure support. This approach is designed to maintain normal FRC and normal WOB. With the recognition of decreased FRC as a principal sequela of general anesthesia and the major role that this pathophysiologic occurrence plays in the development of postoperative complications, it is surprising that the previously mentioned therapeutic approaches have not been routinely utilized in the operating room. In contrast, ventilation of such patients in the operating room typically uses full mechanical ventilation with low tidal volumes, no PEEP, and no pressure support. Spontaneous ventilation is frequently not allowed, owing to concerns with regard to FRC, WOB, and alveolar ventilation. The article by Christie and Smith (1) in this issue of *Anesthesia & Analgesia* addresses some of these concerns.

By monitoring airway pressure, esophageal (pleural) pressure, and air flow, Christie and Smith (1) measured WOB in nine patients during general endotracheal anesthesia and spontaneous ventilation. Each patient was studied under three different ventilatory conditions: a standard anesthesia circle system, a servocontrolled ventilator with demand flow ventilation, and a servocontrolled ventilator with 5 cm H_2O PSV. In anesthetized patients breathing through circle or demand flow systems, WOB was two- to threefold higher than normal. The addition of 5 cm H_2O PSV reduced WOB to normal. There were no differences in hemodynamics or respiratory variables during the three modes of ventilation.

The increased inspiratory WOB during general endotracheal anesthesia can be considered the sum of three components: mechanical ventilatory work needed to overcome the elastic and flow-resistance properties of the lungs and thorax; work required owing to the resistance of the endotracheal tube; and work required owing to the resistance of the ventilator system. Both general anesthesia and endotracheal intubation without PEEP result in decreases in FRC that decrease pulmonary compliance and increase airways resistance. The resistance of an endotracheal tube is related to tube diameter and length (4). A 7-mm endotracheal tube will increase WOB by approximately 30 mJ/L. The increased work required owing to the breathing system varies with the specific demand valves, flow rates, and inspiratory trigger level (5). In the study by Christie and Smith (1), WOB was not divided into its three components. Brochard et al. (6) recently reported data that does provide such a division in patients with respiratory failure. During spontaneous ventilation with a Siemens Servo 900C ventilator, WOB was 1070 mJ/L; during T-piece ventilation, WOB decreased to approximately 900 mJ/L; after tracheal extubation, WOB further decreased to 810 mJ/L. The level of support required to balance the additional WOB due to the endotracheal tube and ventilator varied from 3.4 to 14.4 cm H_2O. In that study, one patient had a 7.5-mm endotracheal tube and all 10 other patients had 8.0–9.0-mm tubes. The use of a smaller endotracheal tube and different ventilator systems in the operating room may result in the need for significantly high levels of pressure support.

In the study by Christie and Smith (1), 5-cm H_2O pressure support decreased WOB but did not affect tidal volumes and respiratory rates. Similar results have been reported by Slee et al. (7) in which increased airway impedance increased WOB but did not affect tidal volumes and respiratory rate during general anesthesia. In both studies, inspiratory time varied to maintain a constant tidal volume; however, other studies indicate that increased airway impedance may result in decreased tidal volumes and minute ventilation. Anesthetized patients frequently breathe at low tidal volumes and minute ventilation owing to the combined effects of decreased pulmonary compliance, increased inspiratory resistance, and the effects of the anesthetic agent. In such situations, the anesthesiologist usually relies on mechanical ventilation to prevent atelectasis and hypercarbia. Pressure support ventilation provides a rational alternative method to achieve adequate tidal volume and alveolar ventilation during spontaneous ventilation. As the current versions of servocontrolled ventilators become more widely available in

the operating room, additional studies will be required to define the benefits of such an approach.

References

1. Christie JM, Smith RA. Pressure support ventilation decreases inspiratory work of breathing during general anesthesia and spontaneous ventilation. Anesth Analg 1992;75:167–71.
2. Viale JP, Annat G, Bertrand O, Godard J, Motin J. Additional inspiratory work in intubated patients breathing with continuous positive airway pressure systems. Anesthesiology 1985;63: 536–9.
3. Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 1988;93:499–505.
4. Bolder PM, Hedy TEJ, Bolder AR, Beatty PCW, Kay B. The extra work of breathing through adult endotracheal tubes. Anesth Analg 1986;65:853–9.
5. Marini JJ, Smith TC, Lamb VJ. External work output and force generation during synchronized intermittent mandatory ventilation. Am Rev Respir Dis 1988;138:1169–79.
6. Brochard L, Rua F, Lorino H, Lemaire F, Harf A. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. Anesthesiology 1991;75: 739–45.
7. Slee TA, Shara SR, Pavlin EG, MacIntyre PE. The effects of airway impedance on work of breathing during halothane anesthesia. Anesth Analg 1989;69:374–8.

Convulsions Associated With Pediatric Regional Anesthesia

Charles B. Berde, MD, PhD

Department of Anesthesia (Pediatrics), Children's Hospital, Boston and Harvard Medical School, Boston, Massachusetts

Regional anesthetic techniques for children have been widely advocated in recent years for postoperative analgesia. A large number of clinical series have reported excellent efficacy and safety (1–4), and several trials have found either improved analgesia or reduced side effects in patients treated with regional analgesia compared with control groups of patients receiving systemic opioids (5,6).

Two reports in this issue of *Anesthesia & Analgesia* alert us to the possibility of systemic toxicity from excessive continuous infusions of local anesthetics in children (7,8). There have been several previous case reports of convulsions or myocardial depression from (presumed intravascular) bolus dosing of local anesthetics (9). A consensus has been reached with regard to the maximal limits for single doses: bupivacaine (2.5 mg/kg) via several routes has produced plasma concentrations in the range of 1–2 μg/mL, which has generally not been associated with a risk of convulsions or myocardial depression in adults.

The authors of the case studies presented in this issue are to be commended for their reporting the complications encountered. This information may help to prevent similar complications from occurring in other patients. In the cases reported here, convulsions were promptly and effectively treated, and no untoward results occurred. Reports of these types of complications rarely appear in the literature.

The observations of the Johns Hopkins group (McCloskey et al. [8]) were initially summarized in a newsletter published by the Society for Pediatric Urology. On the basis of this report and a related series of cases reported by members of the Society for Pediatric Anesthesia, a group of pediatric anesthesiologists chose to pool data concerning pediatric regional anesthetic complications and to develop a multicenter data base. This effort has been funded by the Anesthesia Patient Safety Foundation. As a result of the reports by Agarwal et al. (7) and McCloskey et al. (8) in this issue, and on the basis of our preliminary analysis of 10 cases of convulsions among more than 20,000 pediatric regional anesthetic procedures in 15 institutions, some generalizations and preliminary recommendations can be made with regard to pediatric regional anesthetic dosing and the risk of convulsions.

1. Children Are Probably Not More "Resistant" to Local Anesthetic Toxicity Than Adults

   The initial optimism expressed by McIlvaine and colleagues (10,11) that children may be "resistant" to systemic toxicity from local anesthetics now appears unfounded. Among the cases of convulsions reported here and the cases reported to our data base for which plasma concentrations are available, the concentrations ranged from 2 to 10 μg/mL. McIlvaine et al. (10,11) reported no convulsions in children receiving interpleural infusions at rates of 0.5–2.5 $mg \cdot kg^{-1} \cdot h^{-1}$, with plasma concentrations ranging from 1 to 7 μg/mL. The absence of convulsions in their series may have been due either to small numbers or to the systemic administration of benzodiazepines (to treat restlessness or inability to sleep [see item 2]). Benzodiazepines may have fortuitously protected some of their patients from convulsions.

   Badgwell et al. (12) found more resistance to central nervous system or cardiac toxicity after rapid bupivacaine infusion in 2-day-old piglets (analogous to 6-wk-old humans) compared with 2-wk-old pigs (analogous to 10-mo-old humans) and 2-mo-old pigs (analogous to 3.5-yr-old humans). These results do not necessarily support the safety of higher infusion rates in human infants or children than in adults because (a) human neonates, unlike piglets, have diminished plasma concentrations of α_1-acid glycoprotein, which binds bupivacaine; (b) with prolonged infusions, the slower clearance of bupivacaine in human infants (13) will lead to higher plasma concentrations than in older patients; and (c) 2-wk-old and 2-mo-old pigs (analogous to older infants and toddlers) were as susceptible to toxicity as adult pigs.

This work was supported by a grant from the Anesthesia Patient Safety Foundation.

Accepted for publication April 10, 1992.

Address correspondence to Dr. Berde, Department of Anesthesia (Pediatrics), Children's Hospital, Boston and Harvard Medical School, 300 Longwood Avenue, Farley 3 South, Boston, MA 02115.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

2. Do Not Rely on Premonitory Symptoms or Signs for Detection of Toxicity

   Although adults frequently report symptoms of minor central nervous system toxicity, younger children may not report these symptoms, and restlessness or agitation due to minor central nervous system toxicity in infants and toddlers may be misinterpreted as pain or "difficulty in adjusting to the hospital environment."

   Because of the lack of premonitory signs, Yaster (personal communication) has suggested using lidocaine instead of bupivacaine for prolonged epidural infusions because routine monitoring of plasma concentrations is readily available in clinical laboratories. This alternative deserves further study.

3. Do Not Exceed Recommended Doses or Infusion Rate

   Clinicians should be strongly encouraged not to exceed maximal recommended local anesthetic infusion rates (cf. item 5) when a child appears agitated or in pain. If the maximal infusion rate is reached, alternatives include (a) adding an epidural or systemic opioid in addition to the local anesthetic infusion; (b) testing catheter location with contrast epidurography or by injection of 2-chloroprocaine (which could produce dense sensory block without significant plasma concentrations); or (c) abandoning the technique in favor of systemic opioids or nonsteroidal antiinflammatory drugs.

   Combined epidural local anesthetic/opioid infusions are widely recommended to diminish the doses and toxicities of either drug. This approach has seemed extremely beneficial in adults (14). Although combination infusions seem reasonable in this regard, it remains unproven whether concomitant administration of opioids alters the risk of local anesthetic toxicity. If opioids are administered in large enough doses to produce hypercarbia or hypoxia, the risk of convulsions from local anesthetics would be increased.

4. Do Not Expect Low-Placed Lumbar or Caudal Epidural Local Anesthetic Infusions to Provide the Sole Analgesia After Surgery in Upper Abdominal or Thoracic Dermatomes

   Several cases of excessive dosing involved attempts to provide epidural analgesia with catheter tips located at lumbar levels for abdominal or thoracic surgery. Our study of 54 children undergoing ureteral reimplantation through low transverse abdominal incisions found that when infusions of bupivacaine 0.125% were adjusted to the minimal effective infusion rate to provide good analgesia (objective pain scale [OPS] score ≤ 2), a mean infusion rate of 0.55 mL·kg^{-1}·h^{-1} (0.69 mg·kg^{-1}·h^{-1}) was required (15). These infusions produced plasma bupivacaine concentrations the next day that averaged 2 μg/mL but ranged up to 3 μg/mL in several cases.

   For abdominal and thoracic surgery, if clinicians are considering the use of epidural local anesthetics, alternatives include (a) cephalad advancement of caudal or lumbar epidural catheters to thoracic levels (3); (b) low catheter placement and use of hydrophilic opioids; or (c) thoracic epidural catheter placement (in skilled hands and with proper weighing of risks and benefits) (1).

Table 1. Dependence of Steady-State Plasma Bupivacaine Concentrations (C_{ss}) on Infusion Rate

Infusion rate (mg·kg^{-1}·h^{-1})	Reference No.	Group maximal C_{ss} (μg/mL)
0.2	2	0.8
0.27	15	2
0.69	15	3
1.25–1.5	10	7

5. For Epidural Bupivacaine Infusions, After a Loading Dose of 2–2.5 mg/kg, Infusion Rates Should Probably Not Exceed 0.4–0.5 mg·kg^{-1}·h^{-1} for Older Infants, Toddlers, and Children, or 0.2–0.25 mg·kg^{-1}·h^{-1} for Neonates

   These recommendations are based on available data relating plasma bupivacaine concentrations to infusion rates, as shown in Table 1, and on consideration of the infusion rates and plasma concentrations described by Agarwal et al. (7) and the convulsions reported to our data base, as described earlier. The recommendation of McCloskey et al. (8) to infuse bupivacaine at rates up to 0.75 mg·kg^{-1}·h^{-1} seems insufficiently conservative because at least three convulsions have occurred in patients with infusion rates of 0.5–0.8 mg·kg^{-1}·h^{-1}.

6. Reduce Infusion Rates Further for Patients With Risk Factors for Seizures

   Among the convulsions reported to date to our data base, the only patients with convulsions who were receiving bupivacaine infusion rates ≤ 0.5 mg·kg^{-1}·h^{-1} had factors that could be expected to either (a) increase uptake into the circulation (e.g., pulmonary arteriovenous malformation in the patient of Agarwal et al. [7] receiving interpleural analgesia), or (b) increase the risk of convulsions at lower plasma concentrations (e.g., a past history of febrile convulsions that occurred during a period of postoperative fever, hypomagnesemia, or hyponatremia associated with free water intoxication).

The occurrence of convulsions as reported here should not dissuade clinicians from using epidural local anesthetic infusions in children. Regional anal-

gesia can be used with excellent safety and efficacy in children. Safe administration requires limiting dosing to acceptable infusion rates, careful physician and nursing assessment, and adherence to systematic protocols. In our hospital over the past 6 yr, more than 1400 children and adolescents have received epidural local anesthetic infusions (primarily bupivacaine 0.1% in combination with fentanyl or hydromorphone) in accordance with these dosing guidelines without convulsion.

References

1. Meignier M, Souron R, Leneel J. Postoperative dorsal epidural analgesia in the child with respiratory disabilities. Anesthesiology 1983;59:473–5.
2. Desparmet J, Meistelman C, Barre J, Saint-Maurice C. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. Anesthesiology 1987;67:108–10.
3. Bosenberg AT, Barry AR, Bland FF, Schulte-Steinberg O, Downing JW. Thoracic epidural anesthesia via caudal route in infants. Anesthesiology 1988;69:265–9.
4. Ecoffey C, Dubousset AM, Samii K. Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. Anesthesiology 1986;65:87–90.
5. Krane EJ, Jacobson LE, Lynn AM, Parrot C, Tyler DC. Caudal morphine for postoperative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 1987;66:647–53.
6. May AE, Wandless J, James RH. Analgesia for circumcision in children. A comparison of caudal bupivacaine and intramuscular buprenorphine. Acta Anaesthesiol Scand 1982;26:331–3.
7. Agarwal R, Gutlove DP, Lockhart CH. Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. Anesth Analg 1992;75:284–6.
8. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. Anesth Analg 1992;75:287–90.
9. Matsumiya N, Dohi S, Takahashi H, Kondo Y, Naito H. Cardiovascular collapse in an infant after caudal anesthesia with a lidocaine-epinephrine solution. Anesth Analg 1986;65: 1074–6.
10. McIlvaine W, Chang JHT, Jones M. The effective use of intrapleural bupivacaine for analgesia after thoracic and subcostal incisions in children. J. Pediatr Surg 1988;23:1184–7.
11. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988; 69:261–4.
12. Badgwell JM, Heavner JE, Kytta J. Bupivacaine toxicity in young guinea pigs is age-dependent and is affected by volatile anesthetics. Anesthesiology 1990;73:297–303.
13. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology, 1988;68:387–91.
14. Fischer RL, Lubenow TR, Liceaga A, McCarthy RJ, Ivankovich AD. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesth Analg 1988;67:559–63.
15. Berde CB, Sethna NF, Yemen TA, Pullerits J, Miler V. Continuous epidural bupivacaine-fentanyl infusions in children following ureteral reimplantation (abstract). Anesthesiology 1990; 73:A775.

Pressure Support Ventilation Decreases Inspiratory Work of Breathing During General Anesthesia and Spontaneous Ventilation

Joan M. Christie, MD, and Robert A. Smith, MS

Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida

Spontaneous ventilation may offer advantages over controlled mechanical ventilation (CMV), but increase in work of breathing may diminish its usefulness. During general anesthesia, respiratory depression and increased work of breathing often preclude spontaneous ventilation, and patients then receive CMV. We compared the inspiratory work of breathing of anesthetized patients who breathed with pressure support ventilation (PSV) with that associated with a demand gas flow and a standard anesthesia circle system. We studied nine consenting patients who underwent general inhaled anesthesia with or without regional supplementation. An anesthesia/ventilator system (Siemens 900D, Solna, Sweden) provided PSV (5 cm H_2O) or demand gas flow during spontaneous inspiration. Gas flow during demand breathing and PSV was initiated when inspiration produced a 2-cm H_2O reduction in airway pressure. An anesthesia machine (Dräger Narkomed 3, Telford, Pa.) provided a gas flow rate of 6 L/min through a standard semiclosed circle system. Airway pressure, airway gas flow rate, and esophageal pressure were continuously transduced, and data or signals were conveyed to a computer. Tidal volume and respiratory rate were computed from the flow curve. The inspiratory work of breathing was calculated as the integral of the area subserved by a plot of esophageal pressure and tidal volume during inspiration. Heart rate and mean arterial blood pressure were recorded, and arterial blood was sampled for gas tension and pH analysis. No differences were found in pHa, $Paco_2$, Pao_2, tidal volume, respiratory rate, heart rate, or mean arterial blood pressure among the three modes of ventilation. Inspiratory work of breathing was less when patients received PSV (171 ± 65 mJ/L) (mean ± SD) compared with breathing with a demand valve (690 ± 231 mJ/L) or circle system (532 ± 160 mJ/L) ($P < 0.05$). Mean airway pressure was more with PSV (5.4 ± 1.0 cm H_2O) than with demand flow (0.1 ± 1.4 cm H_2O) or with the circle system (0.4 ± 1.0 cm H_2O) ($P < 0.05$); FIO_2 remained constant at 0.4 ± 0.05. We conclude that PSV with 5 cm H_2O can be used to decrease inspiratory work in spontaneously breathing patients during general anesthesia compared with spontaneous breathing with a standard circle system or demand gas flow and that the reduction is not associated with deleterious hemodynamic effects.

(Anesth Analg 1992;75:167–71)

Work of breathing (WOB) is increased in spontaneously breathing intubated patients undergoing general anesthesia (1,2). When WOB under anesthesia becomes excessive, respiratory failure may result (3,4). The factors that contribute to increased WOB under anesthesia are related to the breathing system used and the effects of the anesthesia itself. The induction of general anesthesia results in reduction of functional residual capacity, decreased lung and thorax compliance, and increased inspiratory resistance (1–6). The breathing system apparatus, including endotracheal tube, valves, connectors, and gas flow rates, also causes increased respiratory tract resistance and WOB (6). In addition to these effects, central ventilatory drive is altered under anesthesia, resulting in varying rate and depth of respiration and displacement of the apneic threshold to a higher Pco_2 level (7). Under these circumstances, anesthesiologists may choose to mechanically control ventilation rather than permit spontaneous breathing. Controlled ventilation in anesthetized patients may produce adverse hemodynamic effects and necessitate paralysis. Spontaneous breathing offers advantages over controlled ventilation with muscle paralysis (e.g., earlier tracheal extubation, stability of arterial blood pressure and heart rate, improved matching of

Presented in part at the Annual Meeting of the International Anesthesia Research Society, March 8–12, 1991, San Antonio, Texas.

Accepted for publication March 4, 1992.

Address correspondence to Dr. Christie, Department of Anesthesiology, University of South Florida College of Medicine, MDC Box 59, 12901 Bruce B. Downs Boulevard, Tampa, FL 33612.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

ventilation and perfusion, and more accurate determination of anesthetic depth) (1,2).

Pressure support ventilation (PSV) is a form of mechanical ventilatory support that delivers a selected amount of positive pressure in response to spontaneous inspiratory effort (8). Studies in nonanesthetized subjects have confirmed the utility of PSV in ameliorating increased resistance imposed by tracheal tubes and ventilator/patient dysynchrony (9). Thus, theoretically, PSV could compensate for some of the increased WOB associated with general anesthesia in spontaneously breathing patients. The effects of PSV on WOB, arterial blood pressure, heart rate, and gas exchange have not been elucidated for anesthetized patients. We compared the inspiratory WOB (W_I), gas exchange, and hemodynamics of anesthetized patients while they spontaneously breathed with a conventional anesthesia circle system, with a demand gas flow, or with 5 cm H_2O of PSV. Our aim was to evaluate the effects of PSV on W_I and to determine whether PSV produced the adverse hemodynamic effects commonly associated with mechanical ventilation.

Methods

Institutional Review Board approval and informed consent from all patients were obtained. Patients scheduled to receive general anesthesia with regional supplementation were premedicated with hydroxyzine HCl (0.6 mg) and midazolam (0.035 mg/kg) intramuscularly. Spinal or epidural blockade was established with 10 mg of tetracaine intrathecally or 20 mL of 0.25% bupivacaine epidurally. Sensory levels were maintained at or below T-7 to minimize the effects of regional anesthesia on respiratory function. One completely paraplegic patient undergoing placement of a penile prosthesis did not receive regional anesthesia. General anesthesia was induced with the intravenous administration of thiopental (2–4 mg/kg) and succinylcholine (2 mg/kg), followed by tracheal intubation with an 8-mm internal diameter tracheal tube. General inhaled anesthesia was maintained with a combination of enflurane/air/oxygen. No opiates or further muscle relaxants were administered. Patients were permitted to breathe spontaneously throughout their operation. If epidural anesthesia was used, bupivacaine (5 mg) was administered every 20 min throughout the operation to provide ongoing analgesia. Inhaled concentrations of enflurane ranged from 0.1% to 1.5%. Mean arterial blood pressure (MAP), heart rate, arterial O_2 saturation, and end-tidal CO_2 were monitored. A pneumotachograph (Fleisch, No. 2, Hewlett-Packard, Fullerton, Calif.) was connected between the tracheal tube and breathing circuit. An 18F gastric tube with an esophageal balloon (Mallinckrodt Anesthesia, St. Louis, Mo.) was inserted into the esophagus. Differential pressure from the pneumotachograph was transduced into AC signals with a differential pressure transducer (DP 1030871; ±2.5 cm H_2O; Validyne, Northridge, Calif.). The signal was converted to DC voltage with a carrier demodulator (CD19A, Validyne). Pressure signals from proximal airway and esophagus were transduced with a low-range differential pressure transducer (MP45-871; ±35 cm H_2O; Validyne) and demodulated with a CD148-871 carrier demodulator (Validyne). All signals were sampled at a rate of 33 Hz with an analogue/digital converter (MC-MIO 16, National Instruments, Austin, Tex.) installed in one of the expansion slots of an IBM PS/2 computer (model 70).

The volume of air inside the esophageal balloon was adjusted from 0.5 to 2.0 mL to maximize inspiratory deflection of esophageal pressure (P_{ES}). The appropriate position of the balloon in the esophagus was verified with the occlusion test previously described (10). The airway opening was occluded while the patient made an inspiratory effort, and positioning was considered adequate when ΔP_{ES} max/ΔPaw max > 0.8, where ΔP_{ES} max is the maximal change in esophageal pressure, and ΔPaw max is the maximal change in airway pressure (Paw).

Patients were randomly assigned in a triple crossover manner to breathe with 5 cm H_2O PSV, a standard anesthesia circle system, and a demand flow circuit. A Siemens anesthesia machine (Servo 900D, Solna, Sweden) was used to deliver PSV and to provide demand flow, and a Dräger anesthesia machine (Narcomed 111, Telford, Pa.) was used for circle system determinations. After patients breathed for 15 min with the assigned mode, analysis and arterial blood gas sampling were performed. Gas tensions, pH, arterial O_2 saturation, heart rate, MAP, and end-tidal CO_2 were recorded.

Airway gas flow, Paw, and P_{ES} signals were stored in computer hard disk memory for off-line analysis of data sampled between the 10th and 15th minute of each breathing modality. Waveforms were replayed, and ventilatory cycles were identified. A ventilatory cycle was defined as the interval between two consecutive moments when flow changed from <50 mL/s to >50 mL/s (T_{TOT}). Starting at the 10th minute of each study period, 25 alternate respiratory cycles were selected for analysis. Atypical waveforms occurring during a cough or sigh were discarded, and remaining waveforms were aligned and averaged. The averaged flow waveform was used to calculate respiratory rate, inspiratory tidal volume (V_T), inspiratory time (T_I), and T_{TOT}. The beginning of respiration was identified as the time of the minimal value of the flow signal during the first 0.45 of the signal (T1). Starting at T1, the local maximal value of the flow integral was sought over 2 s (Figure 1). The time of

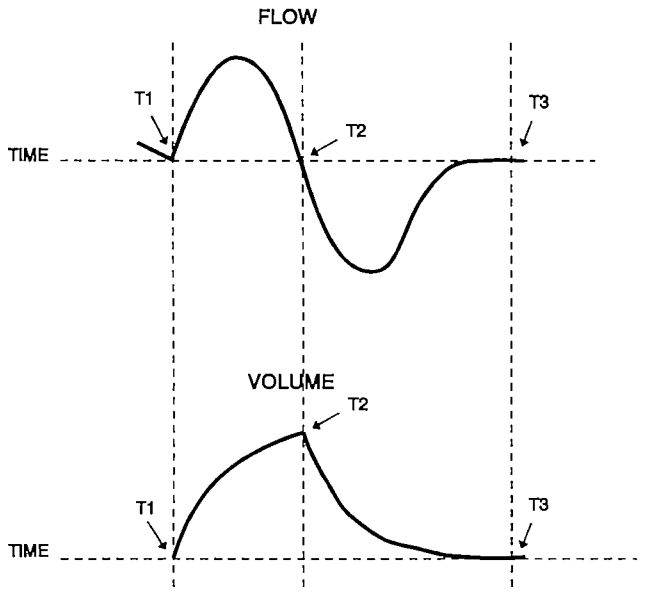


Figure 1. Scheme of a respiratory cycle flow waveform and the integral of flow (tidal volume).

the last maximal value was considered the inspiration endpoint (T2). The interval from T2 until the end of the waveform during expiration was searched for (T3); T3 was the time when flow either passed from a negative to a positive value or when a minimum in the flow integral was found (whichever occurred first). Inspiratory time was calculated as T2 − T1, and total time cycle time as T3 − T1 (T_{TOT}). Inspiratory V_T was obtained from the integration of gas flow between T1 and T2. To calculate change in P_{ES} (ΔP_{ES}) for demand valve or circle systems, the maximal value of the averaged P_{ES} waveform between the beginning of the waveform and T1 was considered as baseline P_{ES}; ΔP_{ES} was determined by subtracting baseline P_{ES} from inspiratory P_{ES} during T1 until T2. For PSV, the value of the averaged P_{ES} waveform at end expiration was considered as baseline P_{ES}; ΔP_{ES} was calculated by subtracting baseline P_{ES} from P_{ES} during T1 until T2. Inspiratory WOB (W_I) (mJ/L) was determined by computer integration of the area under the curve (ΔV_T ΔP_{ES}) during inspiration.

Results are summarized as mean ± SD. Statistical comparisons were made with an analysis of variance for repeated measurements within group design. When an F-value indicated a significant difference between means, a post hoc evaluation was performed to identify differences with Scheffé's test.

Results

We studied nine adult male patients aged 62 ± 15 yr, ASA physical status I–III. Patient characteristics are summarized in Table 1. Operations were relatively long. They lasted 3.5 ± 1.4 h (Table 2), and patients breathed a mixture of enflurane (0.1%–1.5%) and oxygen (F_{IO_2} 0.4 ± 0.05) balanced with air. Regional anesthesia was established before induction of general anesthesia in eight patients, and the ninth patient was paraplegic. The dermatomal sensory levels achieved ranged from T-10 to T-7. Heart rate, MAP, respiratory rate, V_T, pHa, and Pa_{O_2} were not significantly different during study periods (Table 2). End-tidal CO_2 and Pa_{CO_2} were similar with all forms of ventilation and at all concentrations of inspired enflurane (Table 2).

Inspiratory time (T_I) and duty cycle (T_I/T_{TOT}) were less ($P < 0.05$) with pressure support ventilation than with any other modality. Mean Paw was highest when patients breathed with PSV than with demand flow or the circle system ($P < 0.05$). End-inspiratory Paw was less with demand flow than with PSV or the circle system (Table 2). Inspiratory WOB (W_I) was significantly less during PSV than during demand flow or circle system ($P < 0.05$) (Figure 2).

Discussion

The WOB under general anesthesia is increased from altered pulmonary mechanics, from the endotracheal tube, and from the anesthesia apparatus. Functional residual capacity (FRC) in recumbent humans is reduced by approximately 0.5 L with the induction of general anesthesia (11). In some patients, FRC may decrease below residual volume in the awake state (5). The reduction in FRC begins within 30 s after induction of anesthesia with thiopental (12), and it occurs with the most commonly used anesthetic agents and techniques (2). If muscle paralysis is induced in recumbent anesthetized subjects, no further reduction in FRC occurs (13). Approximately 20 min after induction of thiopental anesthesia in supine subjects, the pressure-volume (P/V) curve of the total respiratory system is shifted, and higher inflating pressures are required to inflate the lungs to a given volume in the anesthetized state than in the awake state (2). During isoflurane anesthesia, the P/V curve of the total respiratory system also is shifted to the right, but to a lesser degree (12). High P/V work appears to reduce ventilatory muscle efficiency (i.e., work of ventilation per muscle O_2 demand) (14). Thus, although the mechanisms underlying the reduction in FRC remain unclear, they may be caused by atelectasis, increased thoracic or abdominal blood volume, increased activity of expiratory or decreased activity of inspiratory muscles, trapping of gas distal to closed airways, increased elastic recoil of the lungs, decreased outward recoil of the chest wall, or a combination of these.

Table 1. Operation and Anesthetic Technique in Nine Male Patients

Pt No.	Operation	Time (h)	Enflurane (%)	Regional technique	Sensory level (dermatome)
1	Transverse colectomy	3.0	0.1–0.5	Epidural	T-9
2	Arthroscopy meniscectomy	2.5	1.0–2.0	Spinal	T-10
3	Penile prosthesis	2.3	1.2–1.5	None	—
4	Pyelolithotomy	5.5	0.2–0.3	Epidural	T-9
5	Hemicolectomy	3.3	1.0–1.5	Spinal	T-8
6	Ileal conduit cystoprostatectomy	6.3	0.5–0.9	Epidural	T-8
7	Nephrectomy	4.0	0.5–0.1	Spinal	T-7
8	Herniorrhaphy varicocelectomy	2.0	0.2–0.4	Spinal	T-7
9	Total knee replacement	3.0	0.4–0.6	Spinal	T-10

Table 2. Hemodynamics, Gas Exchange, and Pulmonary Mechanics While Patients Were Breathing With a Circle (Circle) System, Demand Flow (Demand) System, and Pressure Support Ventilation (PSV)

Variable	Circle	Demand	PSV
HR (beats/min)	63 ± 8	64 ± 8	65 ± 8
MAP (mm Hg)	82 ± 18	80 ± 19	79 ± 14
RR (breaths/min)	16 ± 4	16 ± 5	15 ± 5
V_T (mL)	358 ± 101	352 ± 90	371 ± 102
pHa	7.33 ± 0.06	7.34 ± 0.03	7.35 ± 0.04
$Paco_2$ (mm Hg)	45 ± 4	44 ± 4	43 ± 6
Pao_2 (mm Hg)[a]	172 ± 43	171 ± 44	166 ± 48
$P_{ET}CO_2$ (mm Hg)	39 ± 5	40 ± 5	38 ± 5
Inspiratory time	1.6 ± 29	1.8 ± 0.4	1.4 ± 38[b]
Duty cycle time	0.39 ± 0.04	0.43 ± 0.05	0.34 ± 0.05[b,c]
End-inspiratory Paw (cm H_2O)	−0.9 ± 0.4	−2.0 ± 1.0[c,d]	−0.5 ± 0.6
ΔPaw (cm H_2O)	3.8 ± 1.5[b,d]	7.1 ± 2.0	8.1 ± 1.2
Mean Paw (cm H_2O)	0.44 ± 1.0	0.08 ± 1.4	5.4 ± 1.0[b,c]

HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; V_T, tidal volume; Paw, airway pressure; ΔPaw, change in airway pressure.
Values are mean ± SD.
[a] F_{IO_2} = 0.4 ± 0.05.
[b] $P < 0.05$ versus demand flow system.
[c] $P < 0.05$ versus circle system.
[d] $P < 0.05$ versus PSV.

The artificial airway may also impose an undesirable P/V workload that contributes to fatigue or ventilator/patient asynchrony. Even in a constant-flow laboratory experiment, the resistance of a standard size tracheal tube (8.0 mm) exceeds the total resistance of the normal respiratory system (15). Low-level (5–10 cm H_2O) PSV has been advocated to relieve WOB in patients spontaneously breathing through a tracheal tube (9), although recent reports suggest that a higher range may be necessary for some patients (16). The criticism of this approach is related to concern that elevation in mean airway pressure may compromise cardiovascular function in susceptible patients. Although a reservoir bag continuous gas flow system with properly functioning valves imposes only modest increases in inspiratory resistance, the anesthesia apparatus may increase resistive work if the equipment malfunctions (6). Demand valve systems may also increase inspiratory work and they must first detect a preselected drop in airway pressure before flow is initiated (17).

We evaluated three different types of gas delivery systems in anesthetized patients. We found that low-level PSV produced several beneficial effects on nine spontaneously breathing patients under general-regional combination anesthesia. Inspiratory time and duty cycle time were less with PSV compared with demand valve circuit or a circle system, suggesting reduced inspiratory load with PSV. Inspiratory WOB was significantly decreased with PSV. Although mean airway pressure was significantly higher with PSV than with other forms, no evidence of hyperventilation was seen with PSV. The $Paco_2$ was similar in all three groups despite quite high enflurane concentrations in some of these relatively older individuals. Respiratory rate, $Paco_2$, and V_I were similar in all three groups, and no deterioration in pulmonary function was evident, even in the long

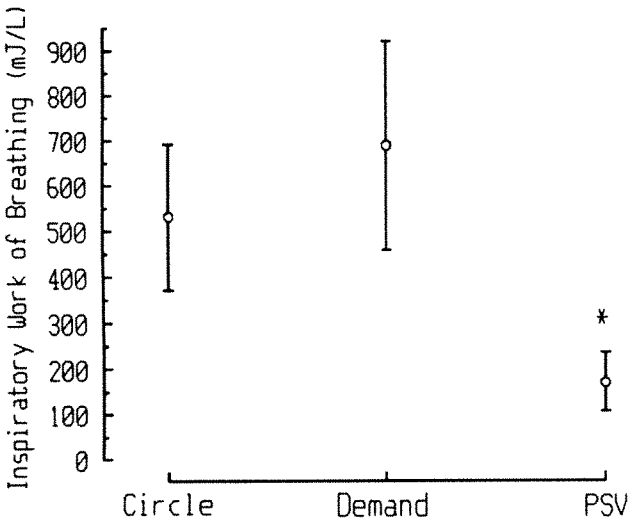


Figure 2. Inspiratory work of breathing during general anesthesia with a standard circle system (Circle), a demand flow system (Demand), and pressure support ventilation (PSV). *$P < 0.05$ versus circle and demand systems.

procedures. No detrimental effects were noted on heart rate or MAP when PSV was compared with demand valve or circle circuit breathing.

Anesthetized patients may undergo profound changes in pulmonary function and rapidly fluctuating hemodynamic status as a result of anesthesia and surgical treatment. The utility of some forms of intensive care unit ventilatory management, such as PSV, have not been firmly established for anesthetized patients. We demonstrated a decreased WOB with PSV in anesthetized patients, consistent with that described for PSV in awake patients (9). The hemodynamic stability that we observed with PSV coupled with the demonstration of decreased WOB supports the efficacy of this technique for patients under anesthesia.

In conclusion, we compared inspiratory WOB in lightly anesthetized patients while they breathed with a conventional circle system, a demand flow circuit, or a pressure support system. Our results demonstrate partial support of spontaneous breathing with 5 cm H_2O of PSV will decrease inspiratory work in spontaneously breathing patients under general anesthesia, without deleterious effects on heart rate or arterial blood pressure, despite a modest increase in mean airway pressure. We conclude that when spontaneous breathing is desirable in patients who require general anesthesia, 5 cm H_2O of PSV will decrease WOB to a level comparable to an unanesthetized state.

References

1. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol 1973;34:81–6.
2. Rehder K, Marsh HM. Respiratory mechanics during anesthesia and mechanical ventilation. In: Fishman AP, Farhi LE, Tenney SM, Geiger SR, eds. Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Bethesda, Maryland: American Physiological Society, 1987:737–52.
3. Bendixen HH, Bullwinkel B, Hedley-Whyte J, Laver MB. Atelectasis and shunting during spontaneous ventilation in anesthetized patients. Anesthesiology 1964;25:297–301.
4. Bendixen HH, Hedley-Whyte J, Chir B, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. N Engl J Med 1963;269:991–6.
5. Don HF, Wahba WM, Craig DB. Airway closure, gas trapping, and the functional residual capacity during anesthesia. Anesthesiology 1972;36:533–9.
6. Trissel LA. Handbook on injectable drugs. Bethesda, Maryland: American Society of Hospital Pharmacists, 1988.
7. Munson ES, Larson CP Jr, Babad AA, Regan MJ, Buechel DR, Eger EI II. The effects of halothane, fluroxene, and cyclopropane on ventilation: a comparative study in man. Anesthesiology 1966;27:716–28.
8. Wahba RWM. Pressure support ventilation. J Cardiothorac Anesth 1990;4:624–30.
9. Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 1988;93: 499–505.
10. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 1964;19:207–11.
11. Bergman NA. Reduction in resting end-expiratory position of the respiratory system with induction of anesthesia and neuromuscular paralysis. Anesthesiology 1982;57:14–7.
12. Don HF, Wahba M, Cuadrado L, Kelkar K. The effects of anesthesia and 100 per cent oxygen on the functional residual capacity of the lungs. Anesthesiology 1970;32:521–9.
13. Hewlett AM, Hulands GH, Nunn JF, Heath JR. Functional residual capacity during anaesthesia II: spontaneous respiration. Br J Anaesth 1974;46:486–94.
14. MacIntyre NR, Leatherman NE. Mechanical loads on the ventilatory muscles: a theoretical analysis. Am Rev Respir Dis 1989;139:968–73.
15. Wright PW, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resistance. Am Rev Respir Dis 1989;140:10.
16. Brochard L, Rua F, Lorino H, Lemaire F, Harf A. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. Anesthesiology 1991;75:739–45.
17. Kirby RR. Continuous positive airway pressure: to breathe or not to breathe. Anesthesiology 1985;63:578–80.

Esmolol Is More Effective Than Sodium Nitroprusside in Reducing Blood Loss During Orthognathic Surgery

William S. Blau, PhD, MD, Enid R. Kafer, MD (Sydney), FRACP, FFARCS, and Jay A. Anderson, DDS, MD

Department of Anesthesiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

The goal of this study was to compare the efficacy of esmolol and sodium nitroprusside (SNP) as primary drugs for producing controlled hypotension and limiting blood loss during orthognathic surgery. Thirty ASA physical status I and II patients (mean age 22 yr) undergoing LeFort I maxillary osteotomies were randomly assigned to receive either esmolol (n = 15) or SNP (n = 15) as the primary drug to induce hypotension. All patients received a balanced anesthetic technique including isoflurane, with controlled hypotension during the downfracture of the maxilla. Patients assigned to the esmolol treatment group received boluses of 500 μg/kg of esmolol, followed by a continuous infusion of 100–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the SNP treatment group received a continuous infusion of SNP at 0.25–4.00 $\mu g \cdot kg^{-1} \cdot min^{-1}$; both infusions were titrated to obtain a mean arterial blood pressure within the target range of 55–65 mm Hg. The mean arterial blood pressure during the hypotensive period was 58.7 ± 0.7 (mean ± SEM) and 61.8 ± 0.4 mm Hg for esmolol and SNP, respectively ($P < 0.001$). In addition, 40% ± 4% of the observed values in the esmolol group and 53% ± 3% in the SNP group were outside the target range for mean arterial blood pressure (difference significant at $P < 0.05$), and a greater proportion of the deviations were above 65 mm Hg in the SNP group than in the esmolol group (0.64 vs 0.46, respectively, $P < 0.05$). The mean heart rate was 70 ± 3 beats/min (esmolol) and 100 ± 3 beats/min (SNP) ($P < 0.001$), and the mean blood loss was 436 ± 65 mL (esmolol) and 895 ± 101 mL (SNP) ($P < 0.001$). The surgical field was judged to be drier with esmolol than with SNP ($P < 0.05$). Plasma renin activity decreased slightly in the esmolol group, whereas in the SNP group it increased 267% ($P < 0.001$). The absence of the renin release may have facilitated the stability of controlled hypotension with esmolol. The advantages of esmolol over SNP for controlled hypotension during orthognathic surgery include greater control of blood pressure, reduction in blood loss, and a drier surgical field. These advantages must be weighed against the possibility of significant myocardial depression produced by intense β_1-adrenergic blockade.

(Anesth Analg 1992;75:172–8)

Induced hypotension is used to help control bleeding during procedures where surgical hemostasis is technically difficult to achieve (e.g., operations on the hip, spine, facial bones, vascular tumors, or arteriovenous malformations). A mean arterial blood pressure (MABP) as low as 50–60 mm Hg appears to be well tolerated in healthy patients (1). Demonstrated benefits of controlled hypotension for orthognathic surgery include a reduction in blood loss, with decreased transfusion requirements and improved quality of the surgical field (2,3).

Various drugs have been used to facilitate the induction of controlled hypotension, including ganglionic blockers (trimethaphan), vasodilators (sodium nitroprusside, nitroglycerin), the combined α- and β-adrenergic antagonist labetalol, and high doses of potent inhaled anesthetics. Although no single drug is considered ideal, the use of sodium nitroprusside (SNP) is well established because of its potency, rapid onset, and short duration of effect. Disadvantages include reflex tachycardia, rebound hypertension, impairment of hypoxic pulmonary vasoconstriction, and the potential for cyanide toxicity at high doses (4–6). Furthermore, a randomized controlled study of

This study was supported by a North Carolina Society of Anesthesiologists Research Fellowship (W.S.B.) and a grant from Du Pont Pharmaceuticals, Wilmington, Delaware.

This study was presented in part at the Annual Meeting of the North Carolina Society of Anesthesiologists, Myrtle Beach, South Carolina, September 1990 and the Annual Meeting of the International Anesthesia Research Society, San Antonio, Texas, March 1991.

Accepted for publication March 11, 1992.

Reprints are not available.

Address correspondence to Dr. Blau, Department of Anesthesiology, CB# 7010, 223 Burnett-Womack Building, University of North Carolina at Chapel Hill, NC 27599-7010.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

patients undergoing orthognathic surgery failed to demonstrate a benefit of SNP-induced hypotension (MABP 55–60 mm Hg) when compared with normotensive controls (MABP 90–100 mm Hg) (7).

Esmolol is a relatively new β_1-selective adrenergic blocker with a rapid onset and a half-life of approximately 9 min that is used for the treatment of supraventricular tachycardia (8). It is also effective in the treatment of perioperative hypertension and to minimize β-sympathetic autonomic responses to noxious stimuli (9) with minimal side effects and no known toxicity. Recent studies have demonstrated its efficacy as an adjunct to SNP (10) and as a primary drug for controlled hypotension (11–13). Its use during orthognathic surgery has not been reported, nor has its effect on blood loss been compared with that of other hypotensive drugs.

The present study was designed to (a) compare the efficacy of esmolol and SNP as primary drugs for reducing arterial blood pressure during orthognathic surgery; and (b) compare their effects on blood loss, duration of surgery, quality of the surgical field, hormonal response, and patient outcome.

Methods

Over a 10-mo period in 1990 we studied 30 ASA physical status I and II patients undergoing LeFort I maxillary osteotomies (usually in combination with mandibular osteotomies) who were randomly assigned to receive either esmolol or SNP as the primary drug for inducing hypotension. Given the known benefits of controlled hypotension (2,3), we chose not to include a normotensive control group so as to avoid subjecting those patients to the risks of unnecessarily high blood loss and the potential need for homologous blood transfusion. The experimental protocol was approved by our Institutional Review Board, and informed consent was obtained from each patient by one of the investigators during the preanesthetic evaluation. Exclusion criteria included any significant systemic illness (including hypertension, history of reactive airways, and central nervous system, cardiac, or renal disorders); age <14 or >40 yr; patient refusal to participate; or in one case, extensive anatomic abnormalities that rendered the procedure unusually long and difficult (patient was excluded after preoperative discussion with the surgical team).

All patients received routine intraoperative monitoring. In addition, a 20-gauge cannula was placed in a radial artery for continuous arterial blood pressure monitoring and serial blood gas and hemoglobin determinations, and a urinary catheter was used to quantify urine output as a guide to fluid management.

All patients were admitted on the day of surgery and received no premedication. Midazolam (0.05 mg/kg IV) was administered for sedation. After baseline systolic blood pressure was recorded (mean of three automatic oscillometric measurements), crystalloid (7 mL/kg), thiopental (3–5 mg/kg IV), and fentanyl (total 5 μg/kg IV by the time of incision) were administered. Vecuronium (0.1 mg/kg IV) was administered to facilitate nasotracheal intubation with a cuffed endotracheal tube, and neuromuscular blockade was maintained with subsequent incremental doses based on the train-of-four twitch response. Ventilation was adjusted to an arterial CO_2 tension ($Paco_2$) of 40 ± 2 mm Hg. Anesthesia was maintained with isoflurane and 65% nitrous oxide in oxygen, and intravenous fluids were titrated to maintain a urine output of 0.5–1.0 $mL \cdot kg^{-1} \cdot h^{-1}$. A few patients received a small supplemental dose of fentanyl or an intramuscular injection of ketorolac (60 mg) at the discretion of the anesthesiologist just before emergence. All but three patients had the endotracheal tube removed in the operating room.

Controlled hypotension was used only during the maxillary osteotomy, with the patient in a 15° reverse Trendelenberg position. In all cases, the surgeons infiltrated the submucosal tissues with 1:100,000 epinephrine to minimize blood loss. Utilizing one of two randomly assigned treatments, MABP was decreased to 75 mm Hg during incision of the maxillary mucosa and was further decreased to 55–65 mm Hg during downfracture of the maxilla until closure of the maxillary mucosa was begun. Patients in the esmolol treatment group received bolus doses of 500 μg/kg of esmolol until MABP was brought within the target range, after which a continuous infusion of 100–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was titrated to maintain hypotension. Patients assigned to the SNP treatment group received a continuous infusion of SNP, beginning at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated to maintain MABP within the target range until the end of the hypotensive period. In both groups, isoflurane up to 2.0% was used to assist in the initiation of hypotension and was maintained at 1.0% throughout the hypotensive period.

Hemodynamic data for each patient were transmitted automatically from the operating room monitor to a computer data base (Hewlett Packard Vectra CareView software program) and were subsequently tabulated by 2-min intervals and analyzed for hemodynamic trend and variability during the hypotensive period. Blood loss was estimated by an observer unaware of the experimental treatment and was based on carefully measured volumes of irrigation solution and fluid/blood aspirated from the surgical field. Direct inspection revealed minimal additional blood on surgical sponges, drapes, or gowns. At the end of the procedure, the quality of the surgical field was rated by the attending surgeon, who was also

unaware of the experimental treatment, using a six-point scale (0 = no bleeding, virtually bloodless field; 5 = massive uncontrolled bleeding) (7). Arterial blood gas samples were obtained at intervals during the procedure to verify the adequacy of ventilation. The calculated base deficit was followed as a marker for adequacy of perfusion and for cyanide toxicity. For a subsample of 10 patients in each treatment group, blood was collected at induction and at the end of the hypotensive period for analysis of plasma renin activity (PRA). The PRA analysis was performed by a radioimmunoassay technique (14) (SmithKline Beecham Clinical Laboratories, Ltd., Atlanta, Ga.). Blood samples were obtained from all patients at the time of the preoperative evaluation and on the day of discharge for determination of hematocrit and serum creatinine.

Student's *t*-test (unpaired) or repeated measures analysis of variance was used for analysis of parametric data (Statistical Analysis Systems, Cary, N.C.). The Wilcoxon rank-sum test was performed on ordinal data or where distributions were clearly not normal. Because distributions of heart rate and MABP for individual patients (i.e., "within" patients) during the hypotensive period were skewed, median values were used to represent the overall trend for each patient. The distribution of median values for heart rate and MABP among patients was not skewed, so comparisons among patients were performed with *t*-tests, and the data comparing treatment groups are presented as mean values ± SE. A probability of type I error of ≤5% ($P \leq 0.05$) was used as the criterion for statistical significance.

Results

Analysis of the patient population and the surgical procedures performed revealed no apparent differences that could lead to statistical bias between the treatment groups (Table 1), and controlled hypotension within the desired range was rapidly and successfully obtained with either esmolol or SNP at low to moderate infusion rates (Table 2). Although MABP decreased within the target range for both groups, the value obtained was slightly higher in the SNP group. There was considerable hemodynamic variability during the hypotensive period, with the most frequently observed MABPs occurring near the lower portion of the target range for patients receiving esmolol and near the higher portion of the target range for patients receiving SNP (Figure 1). There was relatively less hemodynamic variability in patients receiving esmolol, with fewer observed MABPs occurring outside the target range, and those occurring outside tended to be lower rather than higher (Table 2). As anticipated, heart rate was significantly lower in the esmolol group than in the SNP group.

Table 1. Characteristics of 30 Patients Undergoing LeFort I Maxillary Osteotomies

	Esmolol group (n = 15)	Sodium nitroprusside group (n = 15)
Patients		
Women (n)	10	11
Age (yr)[a]	22 (14–37)	22 (15–40)
Weight (kg)[a]	64 (47–82)	63 (48–100)
Baseline systolic blood pressure (mm Hg)[a,b]	123 (101–148)	123 (110–135)
Procedure		
LeFort I		
No. of maxillary cuts (n)		
1	8	12
2	4	1
3	3	2
+mandibular osteotomy (n)	11	11
+other procedure (n)[c]	3	6
Technical difficulty[d]		
Easy (n)	2	4
Moderate (n)	7	7
Difficult (n)	6	4

[a]Mean value (range).
[b]Baseline systolic blood pressure obtained after intravenous sedation and before induction of anesthesia.
[c]Genioplasty, bone harvest, etc.
[d]As rated by the attending surgeon.

Table 2. Doses and Hemodynamic Effects of Drugs Used for Controlled Hypotension in the Two Study Groups

	Esmolol group	Sodium nitroprusside group	Statistical significance[b]
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)[a]	160 (100–300)	1.75 (0.25–4.0)	
Total dose (mg)	1072 ± 99	10.5 ± 1.9	
Delay in onset of hypotension (min)	3.7 ± 1.1	3.1 ± 0.9	NS
MABP (mm Hg)	58.7 ± 0.7	61.8 ± 0.4	$P < 0.001$
MABP outside target range (%)[c]	40 ± 4	53 ± 3	$P < 0.05$
Proportion of high deviations	0.46 ± 0.08	0.64 ± 0.03	$P < 0.05$
Heart rate (beats/min)	70 ± 3	100 ± 3	$P < 0.001$

NS, not significant; MABP, mean arterial blood pressure.
Results are mean values ± SE unless otherwise indicated.
[a]Median (range).
[b]For treatment effect, esmolol vs nitroprusside (Student's *t*-test).
[c]Target range, MABP 55–65 mm Hg.

There was no significant difference in the duration of surgery or the duration of hypotension between the treatment groups (Table 3). The surgeons generally rated bleeding as mild to moderate, and the field was rated drier in the esmolol group ($P < 0.05$).

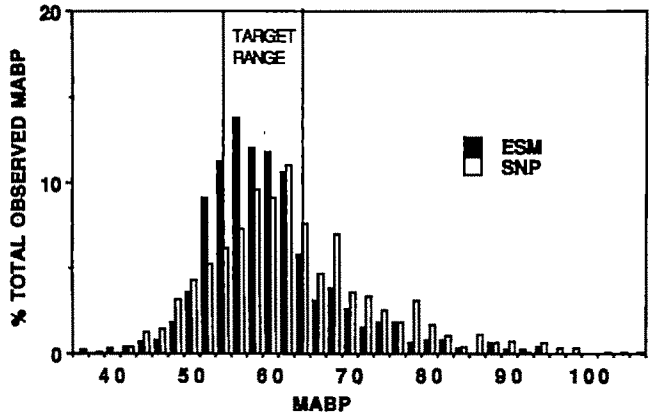


Figure 1. Average frequency distributions for mean arterial blood pressure (MABP) in patients receiving esmolol (ESM) or sodium nitroprusside (SNP) for controlled hypotension. Target range for MABP was 55–65 mm Hg.

Table 3. Duration of Surgery, Quality of the Surgical Field, and Blood Loss in the Two Study Groups

	Esmolol group	Sodium nitroprusside group	Statistical significance[b]
Duration of surgery (min)	214 ± 25	215 ± 15	NS
Duration of hypotension (min)	95 ± 7	95 ± 9	NS
Surgical field rating[a]	1 (1–2.5)	2 (0–4)	$P < 0.05$[c]
Estimated blood loss (mL)			
During hypotension	304 ± 48	650 ± 110	$P < 0.01$
Total	436 ± 65	895 ± 101	$P < 0.001$

NS, not significant.
Results are mean values ± SE unless otherwise indicated.
[a]Median (range); rating scale is 0–5, where 0 = no bleeding, virtually bloodless field, and 5 = massive uncontrollable bleeding (Reference 7).
[b]For treatment effect, esmolol vs nitroprusside (Student's *t*-test).
[c]Wilcoxon two-sample test.

Furthermore, total measured blood loss in the esmolol group was 49% of that in the SNP group (436 vs 895 mL, respectively; $P < 0.001$). To determine whether this difference was related to the degree of hemodynamic variation during hypotension, we examined the relationship between blood loss during hypotension and the frequency with which MABP was above the target range in patients receiving SNP (Figure 2). There was no increase in blood loss with increased frequency of high blood pressure.

The effect of controlled hypotension on PRA is illustrated in Figure 3. The PRA decreased slightly during hypotension in the esmolol treatment group and increased 267% in the SNP treatment group.

Perioperative changes in plasma acid-base balance are illustrated in Figure 4. Although there was a trend toward development of a mild base deficit during the

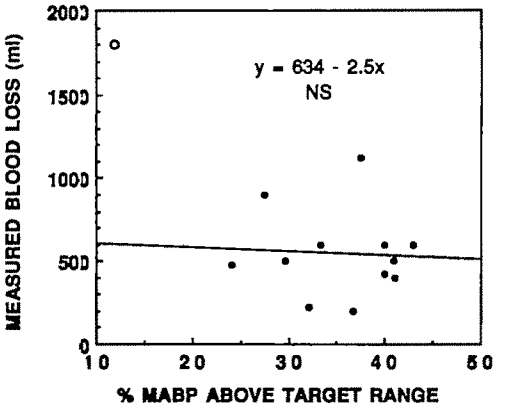


Figure 2. Scatter plot of measured blood loss during hypotension as a function of the frequency of high arterial blood pressures (percent observed mean arterial blood pressure [MABP] for each patient occurring above the target range of 55–65 mm Hg). One patient was eliminated because the hemodynamic data were accidentally lost, and an additional outlying data point (12% × 1900 mL, *open circle*) was excluded from the least-squares regression analysis. NS, not significant.

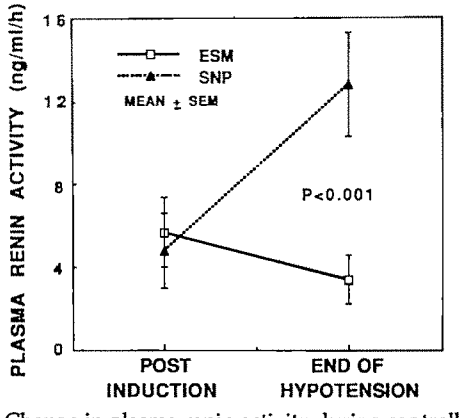


Figure 3. Change in plasma renin activity during controlled hypotension for patients receiving esmolol (ESM) or sodium nitroprusside (SNP). Data are mean values ± SEM for blood samples at baseline (after induction but before the onset of hypotension) and at the end of the hypotensive period. The difference in response between treatments is highly significant ($P < 0.001$ for interaction effect, repeated measures analysis of variance).

operative period, there were no significant differences between treatment groups. A number of patient outcomes were also examined to detect any side effects or differences in safety between the two treatment groups (Table 4). We failed to detect any differences, with the exception of a slight but significant reduction in serum creatinine in the SNP group. There were no postoperative complications in either group, and all patients were discharged between the first and third postoperative days.

Discussion

We have demonstrated that esmolol is as effective as SNP in reducing arterial blood pressure for controlled

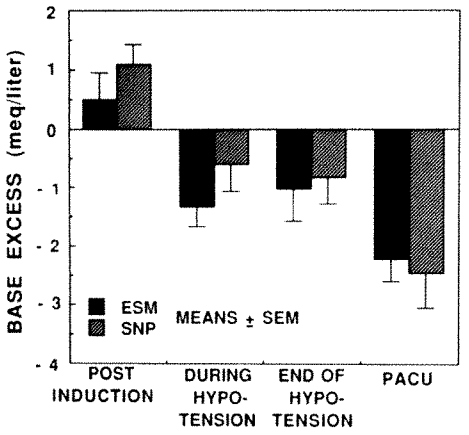


Figure 4. Perioperative base deficits for patients receiving esmolol (ESM) or sodium nitroprusside (SNP) for controlled hypotension, as determined by arterial blood gas analysis. Data are mean values ± SEM. Samples were collected after induction but before onset of hypotension (baseline), after 30 min of controlled hypotension, at the end of the hypotensive period before arterial blood pressure was allowed to rise, and on arrival in the postanesthetic care unit (PACU). The change in the deficit over time is significant ($P < 0.001$), but there is no difference between treatment groups (repeated measures analysis of variance).

hypotension during orthognathic surgery. This finding is consistent with the results of previous studies involving other types of surgery (11–13,15). Esmolol lowers arterial blood pressure through a decrease in cardiac output secondary to the negative chronotropic and inotropic effects of β_1-adrenergic antagonism (12,13,16). In addition, it may produce direct myocardial depression at very high doses (e.g., >500 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (8). Esmolol provided a more stable course of controlled hypotension than did SNP, with a slightly lower MABP and fewer deviations from the target arterial blood pressure range. Hemodynamic stability in this case may result from the inhibition of autonomically mediated secretion of renin (10,13,17) and the attenuation of other compensatory hormonal responses known to occur during controlled hypotension with SNP or isoflurane (10,18–20); β_1-adrenergic blockade will also prevent reflex autonomic increases in heart rate in response to the vasodilation produced by isoflurane.

Our results demonstrated a considerable degree of hemodynamic variability during controlled hypotension, but there are no other published data on arterial blood pressure variation within patients with which to draw any comparison. Factors limiting the precision of arterial blood pressure control are likely to include minute-by-minute variations in the degree of surgical stimulation and of intravascular volume status and lag times in the pharmacologic response to alterations in arterial blood pressure.

Direct comparison of blood loss among studies is difficult because of differences in surgical duration, technique, and the timing of controlled hypotension. Nevertheless, the total blood loss in our SNP group (895 mL) was similar to that reported by Fromme et al. (7) for patients undergoing similar procedures with SNP-induced hypotension (828 mL) or without controlled hypotension (965 mL) and to that reported by Lessard et al. (2) for their normotensive control group (755 mL). In contrast, blood loss in our esmolol group was comparable to that reported for other hypotensive techniques in orthognathic surgery (mean of 454 mL with isoflurane alone; 399 mL with labetalol; 439 mL with nitroglycerin) (2,21,22). One possible reason for increased blood loss with SNP could be the greater hemodynamic instability with this drug, leading to a higher frequency of high arterial blood pressures; however, closer examination of our data for patients receiving SNP revealed no correlation between blood loss and the proportion of observed MABPs above the desired range (Figure 2). Another possible explanation for increased bleeding could be the larger cardiac output with SNP, although there is evidence that blood loss during hypotension is not dependent on cardiac output (23). Lessard et al. (2) suggest that different techniques for inducing hypotension may have different effects on the vascular beds involved in maxillary osteotomies. Perhaps SNP selectively dilates these beds. The adverse effect of SNP on platelet function and bleeding time (24) may also compromise hemostasis during surgery.

The differences in blood loss between the treatment groups would suggest that the drop in postoperative hematocrit should be greater for patients who received SNP. This was observed (Table 4), although the difference between the treatment groups only approached significance ($P = 0.066$). The transfusion practices for patients in this study may have tended to obscure differences in postoperative hematocrit. All patients had deposited autologous blood preoperatively. Owing to the perceived safety of reinfusion of autologous blood, the oral surgeons did not use uniform criteria for postoperative transfusion; indeed, many patients received transfusion postoperatively before documentation of the postoperative hemoglobin concentration. It is reasonable to expect that a reduction of 50% in blood loss, as demonstrated with esmolol, would reduce the incidence of transfusion if the latter were guided by more stringent criteria based on hemoglobin concentration. This would improve patient safety, as even the reinfusion of autologous blood is not without risk (25).

Esmolol has a brief duration of action, promotes hemodynamic stability, and produces beneficial effects in the surgical field and in blood conservation. For these reasons, it may be preferred as a primary drug for inducing hypotension in healthy patients undergoing orthognathic surgery. In the present study, no apparent adverse side effects occurred

Table 4. Patient Outcomes in the Two Study Groups

	Esmolol group	Sodium nitroprusside group	Statistical significance[b]
Intraoperative			
Total fluid (mL)	3277 ± 213	3577 ± 266	NS
Urine output (mL)	340 ± 58	403 ± 64	NS
No. of Pts extubated in OR/total	12/15	15/15	NS[c]
Postanesthesia care unit			
Admission score[a]	8 (7–9)	9 (7–9)	NS[d]
Time to discharge (min)	122 ± 7	130 ± 9	NS
SABP on admission (mm Hg > baseline)	8 ± 3	15 ± 4	NS
Total fluid (mL)	269 ± 53	327 ± 42	NS
Urine output (mL)	145 ± 45	183 ± 47	NS
Postoperative			
Change in creatinine from preop (mg/dL)	−0.08 ± 0.02	−0.18 ± 0.3	$P < 0.05$
Change in hematocrit from preop	−6.6 ± 1.2	−10.0 ± 1.3	NS
No. of Pts transfused/total	8/14	9/15	NS[c]
Day of discharge (postop)	2.1 ± 0.2	2.0 ± 0.2	NS

NS, not significant; OR, operating room; Pts, patients; SABP, systolic arterial blood pressure.
Results are mean values ± SE unless otherwise indicated.
[a]Median (range).
[b]For treatment effect, esmolol vs nitroprusside (Student's *t*-test).
[c]Fisher's exact test.
[d]Wilcoxon two-sample test.

when esmolol was used to lower MABP to 55–65 mm Hg for up to 165 min in healthy patients. Caution is indicated, however, as profound myocardial depression may result from its use (13). There is some preliminary evidence that esmolol infusion at rates >200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may be deleterious to total body oxygen balance (26), although the same may also be true for therapeutic doses of SNP (27). Nevertheless, the most significant risks are probably those shared by all hypotensive techniques, and with proper patient selection and vigilant monitoring, esmolol can be used safely. Based on our results and a review of the literature, we make the following recommendations for minimizing blood loss and optimizing safety during orthognathic surgery: (a) esmolol may be used as a primary hypotensive drug in healthy patients; (b) the degree of hypotension should be titrated to observed blood loss (extremes of hypotension may not be required); (c) when using esmolol alone to produce hypotension as low as 60 mm Hg, cardiac output should be monitored; and (d) esmolol should be used in combination with other hypotensive drugs to limit the doses required.

We thank Dr. Robert Valley for commenting on the manuscript. This work was facilitated by the cooperation and assistance of Donna Snead-Bruce, RN, Ricky D. Hunt, BS, and the resident and attending staff of the Departments of Anesthesiology and of Oral and Maxillofacial Surgery of the University of North Carolina at Chapel Hill.

References

1. Anderson JA. Deliberate hypotensive anesthesia for orthognathic surgery: controlled pharmacologic manipulation of cardiovascular physiology. Int J Adult Othodon Orthogn Surg 1989;1:134–59.
2. Lessard MR, Trepanier CA, Baribault JP, et al. Isoflurane-induced hypotension in orthognathic surgery. Anesth Analg 1989;69:379–83.
3. Chan W, Smith DE, Ware WH. Effects of hypotensive anesthesia in anterior maxillary osteotomy. J Oral Surg 1980;38: 504–8.
4. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
5. Khambatta HJ, Stone JG, Khan E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.
6. Wildsmith JAW, Drummond GB, MacRae WR. Blood-gas changes during induced hypotension with sodium nitroprusside. Br J Anaesth 1975;47:1205–10.
7. Fromme GA, MacKenzie RA, Gould AB, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery. Anesth Analg 1986;65:683–6.
8. Gorczynski RJ. Basic pharmacology of esmolol. Am J Cardiol 1986;56:3F–13F.
9. Menkhous PG, Reves JG, Kissin I, et al. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.
10. Edmondson R, Del Valle O, Shah N, et al. Esmolol for potentiation of nitroprusside-induced hypotension. Impact on the cardiovascular, adrenergic, and renin-angiotensin systems in man. Anesth Analg 1989;69:202–6.
11. Blair JL, McGuire R, Killian J, Amundson G. Esmolol as primary agent for controlled hypotension (abstract). Anesth Analg 1989;68:S31.
12. Ornstein E, Matteo RS, Weinstein JA, Schwartz AE. A con-

trolled trial of esmolol for the induction of deliberate hypotension. J Clin Anesth 1988;1:31–5.
13. Ornstein E, Young WL, Ostapkovich N, Matteo RS, Diaz J. Deliberate hypotension in patients with intracranial arteriovenous malformations. Esmolol compared with isoflurane and sodium nitroprusside. Anesth Analg 1991;72:639–44.
14. Sealy JE, Laragh JH. Radioimmunoassay of plasma renin activity. Semin Nucl Med 1975;5:189–202.
15. Del Valle O, Edmondson R, Reinsel R, Shah N, Herr H, Bedford R. Esmolol vs nitroprusside for hypotension: dose response during isoflurane anesthesia (abstract). Anesthesiology 1990;72:A143.
16. Acampora G, Shah N, Del Valle O, Edmondson R, Bedford R. Myocardial depression by esmolol during nitroprusside hypotension (abstract). Anesthesiology 1989;71:A19.
17. Buhler FR, Laragh JH, Baer L, Vaughn DE, Brunner HR. Propranolol inhibition of renin secretion. N Engl J Med 1972; 287:1209–14.
18. Zubrow AB, Daniel SS, Stark RI, Husain MK, James LS. Plasma renin, catecholamine, and vasopressin during nitroprusside-induced hypotension in ewes. Anesthesiology 1983; 58:245–9.
19. Bernard JM, Pinaud M, Maquin-Mavier I, Remi JP, Passuti N. Hypotensive anesthesia with isoflurane and enflurane during total hip replacement: a comparative study of catecholamine and renin angiotensin responses. Anesth Analg 1989;69:467–72.
20. Dickstein ML, Jordan DA, Miller ED. Esmolol ablates the adrenal medullary response to hypotension (abstract). Anesthesiology 1990;73:A547.
21. McNulty S, Sharifi-Azad S, Farole A. Induced hypotension with labetalol for orthognathic surgery. J Oral Maxillofac Surg 1987;45:309–11.
22. Golia JK, Woo R, Farole A, Seltzer J. Nitroglycerin-controlled circulation in orthognathic surgery. J Oral Maxillofac Surg 1985;43:342–5.
23. Sivarajan M, Amory DW, Everett GB, Buffington C. Blood pressure, not cardiac output, determines blood loss during induced hypotension. Anesth Analg 1980;59:203–6.
24. Hines R, Barash PG. Infusion of sodium nitroprusside induces platelet dysfunction in vitro. Anesthesiology 1989;70:611–5.
25. Miller AC, Scherba-Krugliak L, Toy PT, Drasner K. Hypotension during transfusion of autologous blood. Anesthesiology 1991;74:624–8.
26. Quinn TJ, Zayas VM, LeDonne K, McDonald M, Pickering T. Esmolol and controlled hypotension: adverse effects on oxygen extraction (abstract). Anesthesiology 1990;73:A94.
27. Endrich B, Franke N, Peter K, Messmer K. Induced hypotension: action of sodium nitroprusside and nitroglycerin on the microcirculation. Anesthesiology 1987;66:605–13.

Long-Term Hypotensive Technique With Nicardipine and Nitroprusside During Isoflurane Anesthesia for Spinal Surgery

Jean-Marc Bernard, MD, Norbert Passuti, MD, PhD, and Michel Pinaud, MD, PhD

Département d'Anesthésie-Réanimation Chirurgicale, Hôtel Dieu, and Clinique d'Orthopédie, Hôpital Saint-Jacques, Nantes, France

Short-term infusion of nicardipine can be used to induce deliberate hypotension but may result in plasma drug accumulation. To assess long-term nicardipine administration for deliberate hypotension in 10 patients in a moderately hemodiluted state who were undergoing spinal surgery, hemodynamics and plasma nicardipine concentrations were concomitantly measured before and 20, 80, and 140 min after starting nicardipine, at drug discontinuation, and 20 and 80 min later. A dose of 6.2 ± 0.9 mg (mean ± SEM) of nicardipine was initially required to obtain mean arterial blood pressures at 55–60 mm Hg. Maintenance doses of nicardipine were 3–5 mg/h. The duration of nicardipine administration was 270 ± 20 min (mean ± SEM). Hypotension was associated with decreased systemic and pulmonary vascular resistances, increased cardiac index, and decreased arteriovenous difference in O_2 contents. Only two patients required homologous blood transfusion. Plasma nicardipine concentrations peaked at 110 ± 21 ng/mL (mean ± SEM) and then decreased to 38 ± 11 ng/mL (mean ± SEM) without changes in arterial blood pressure. After vasodilator discontinuation, hypotension was observed during a mean time of 43 min (range 27–88 min) despite plasma concentrations <20 ng/mL. No relationship was found between plasma nicardipine concentrations and hemodynamics. These findings suggest that an increasing effect of nicardipine over time may occur during prolonged administration. Because the reasons for this hysteresis remain unclear, use of nicardipine infusion during major surgery and anesthesia requires particular caution.

(Anesth Analg 1992;75:179–85)

In elderly patients undergoing total hip arthroplasty, 4–12 mg/h of intravenous nicardipine, a dihydropyridine calcium channel blocker, can be used to cause deliberate hypotension (1). The delayed return to a normal arterial blood pressure after nicardipine discontinuation (mean time >60 min) was due to plasma nicardipine accumulation (i.e., mean concentration >200 ng/mL) despite relatively short-term administration (1). This accumulation may be of concern if a rapid return to normal arterial blood pressure is desirable. The use of nicardipine to induce deliberate hypotension under anesthesia is thus questionable, especially during long-term administration. Despite this, and given the risk of cyanide toxicity of nitroprusside (2), it is during long-term hypotensive techniques that an alternative to nitroprusside may be of particular value.

This current study was designed to compare long-term nicardipine- and nitroprusside-induced hypotension. Plasma nicardipine concentrations were determined concomitantly with hemodynamic measurements in all patients. Isoflurane anesthesia was selected because it is widely used for inhaled hypotensive anesthesia, and its effect on hemodynamic properties and disposition of dihydropyridine calcium channel blockers is well documented (3–5).

Methods

This study was approved by our Human Investigation Committee. After informed consent was obtained, 20 ASA physical status I and II patients (12 men, 8 women) were studied. They underwent extensive posterior thoracolumbar spinal fusion for idiopathic scoliosis. Patients were excluded from the study if they had a history of coronary artery disease,

This work was supported in part by the University of Nantes Institutional Grant Program.

This work was presented in part at the 1990 Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada.

Accepted for publication March 31, 1992.

Address correspondence to Dr. Bernard, Département d'Anesthésie-Réanimation Chirurgicale, Hôtel-Dieu, 44035 Nantes Cédex 01, France.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

congestive heart failure, hypertension (i.e., arterial blood pressure >140/95 mm Hg), or hepatic or renal insufficiency. Correction of scoliosis was obtained in all patients by means of Cotrel Dubousset instrumentation with bilateral rods through variable vertebral hooks and corticocancellous bone grafts taken from the iliac crest. All operations were performed by one surgeon using the same technique. Patients were positioned prone on a specially designed form mattress in which a hole had been cut to allow the entire abdomen to hang free of the table.

Monitoring included a DII and V_5 electrocardiogram lead (Sirecust 960, Siemens), an indwelling radial artery catheter, and a fiberoptic pulmonary artery thermodilution catheter (Opticath Oximetrix, Abbott). Anesthetic technique consisted of oral premedication with diazepam (10 or 15 mg according to body weight: <70 or >70 kg). Induction of anesthesia was performed with thiopental (5 mg/kg IV) and alfentanil (50 μg/kg IV), followed by vecuronium bromide (0.1 mg/kg IV) to facilitate tracheal intubation. No atropine was administered. Lungs were mechanically ventilated with an isoflurane-O_2-N_2O mixture (inspired oxygen concentration [F_{IO_2}], 0.5). Ventilation was adjusted to maintain end-tidal CO_2 partial pressure between 32 and 40 mm Hg, with a respiratory rate of 16 breaths/min and an I/E ratio of 1:2. Isoflurane was adjusted to maintain a steady end-tidal concentration equal to 0.6 vol% throughout the procedure, except for a wake-up test just after distraction of the spine. End-tidal concentration was measured by an infrared analyzer calibrated with a known standard. Alfentanil was continuously infused at a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from the start of anesthetic induction until the first rod was positioned. Isoflurane was discontinued just after skin closure.

At surgical incision, nicardipine (20 mg in 40 mL of 5% dextrose) or nitroprusside (concentration 100 mg/L) was infused at random through a Teflon antecubital cannula used only for this purpose. In the nitroprusside group (n = 10), infusion was initiated at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased every 1 min by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until either mean arterial blood pressure (MAP) was reduced to 55–60 mm Hg or a dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was reached. In the nicardipine group (n = 10), according to the results of the Lambert et al. study (6), the infusion was started at a rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and continued until MAP was at a level of 55–60 mm Hg, at which time it was decreased to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. For each vasodilator, the infusion rate was modulated according to the arterial blood pressure response, and a maintenance dose was administered to stabilize MAP at 55–60 mm Hg until muscle and skin closure were started. The surgeon was unaware of the type of vasodilator used.

During the surgical procedure, a polygeline (Plasmion) was infused to establish an initial hemodiluted state. Polygeline is an oncotically active gelatin with a molecular weight between 30,000 and 40,000 and an effective half-life of 4–6 h. Hematocrit was maintained in the 26%–30% range until skin closure by red blood cells. Autologous red blood cells were obtained from the patient before surgery (1 U/wk for 1 mo) and stored in the conventional way. During the operation, autotransfusion was performed by aspiration of blood from the operation site. The same blood was filtered, washed, and reinfused (Autotrans BT 795/P, Dideco). Blood loss was assessed by weighing sponges, measuring suction drainage, and estimating the amount of blood in the area of the wound.

Heart rate, systolic and diastolic arterial pressure, right atrial pressure, systolic and diastolic pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac output (iced injectate in triplicate), and O_2 saturation of mixed venous blood ($S\bar{v}O_2$), as well as arterial O_2 tension (P_{O_2}), arterial CO_2 tension (P_{CO_2}), pH, O_2 saturation (S_{O_2}), and hemoglobin in arterial and mixed venous blood, were measured at the following times: at baseline before hypotension; 20, 80, and 140 min after starting nicardipine and nitroprusside; at the end of hypotension (vasodilator discontinuation); and 20 min later. All data were measured in patients in the prone position during stable isoflurane anesthesia (end-tidal concentration 0.6%). A final measurement was performed 80 min after vasodilator discontinuation when isoflurane was discontinued and therefore not detectable by the infrared analyzer. At each time, arterial blood samples were drawn for determination of plasma nicardipine concentrations (Sandoz Laboratory, France) by gas chromatography using an electron capture detector (7). The interday reproducibility was equal to 11.8% at 5 ng/mL and 6.8% at 75 ng/mL. The response was linear, at least between 0 and 200 ng/mL. The limit of quantification was 0.5 ng/mL. The electrocardiogram lead and $S\bar{v}O_2$ were continuously recorded. Derived values, such as MAP, mean pulmonary arterial pressure (MPAP), cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index, arteriovenous difference in O_2 contents, O_2 consumption index, O_2 extraction ratio, and intrapulmonary shunt fraction were computed according to standard formulas (8,9).

Comparisons were made by analysis of variance for repeated measurements when the two factors were treatment (nicardipine and nitroprusside) and time. When F-statistic was significant, multiple comparisons within and between groups were performed after Bonferroni corrections. Unpaired t-tests were

Table 1. Clinical Characteristics and Procedural Summary for 20 Patients Undergoing Spinal Surgery

	Nicardipine group (n = 10)	Nitroprusside group (n = 10)
Age (yr)	32 ± 3	27 ± 4
Gender (F/M) (n)	6/4	6/4
Weight (kg)	58 ± 3	52 ± 2
No. of vertebrae fused	13.9 ± 1.4	13.9 ± 0.8
Duration of vasodilator administration (min)	270 ± 20	230 ± 14
Blood loss (mL)		
Sponges	1540 ± 160	1790 ± 450
Suction	3580 ± 350	4380 ± 960
Cumulative red blood cells (mL)	1920 ± 250	2580 ± 610
Cumulative polygeline (mL)	3130 ± 390	3310 ± 580
Patients receiving autologous blood (n)		
Only from aspiration	2	1
From aspiration and bank	6	6
Patients receiving homologous blood (n)	2	3

F, female; M, male.
Results are expressed as mean ± SEM. There were no significant differences between groups

used to compare demographic data, duration of vasodilator administration, blood loss, cumulative red blood cells, and polygeline. One-way analysis of variance, followed by a Newman-Keuls test was used for maintenance nicardipine and nitroprusside infusion rates and for plasma nicardipine concentration. To assess the relationship between hemodynamic changes and plasma nicardipine concentration, data were fitted to a linear model; α was set at a level of 0.05. Data are presented as mean ± SEM.

Results

No differences were observed between groups with respect to age, sex, weight, and duration of vasodilator administration. Blood loss, cumulative amounts of red blood cells, and polygeline were not significantly different between groups (Table 1).

The desired level of hypotension was obtained in a mean time of 9 min (range 7–13 min) in the nitroprusside group and 11 min (range 5–17 min) in the nicardipine group. No patients were eliminated from the study for exceeding the nitroprusside dose limitations discussed earlier. Nicardipine (6.2 ± 0.9 mg) was initially required to decrease MAP to 55–60 mm Hg. Hypotension was then maintained at this level with a significantly decreasing infusion rate in the nicardipine group and a stable infusion rate in the nitroprusside group (Table 2). Cumulative doses of nicardipine and nitroprusside were, respectively, 18 ± 2 and 45 ± 10 mg. All patients received a dose of nitroprusside <1.5 mg/kg.

In both groups, hypotension was associated with decreased systemic and pulmonary vascular resistances, increased CI, and decreased arteriovenous difference in O_2 contents and pH, but no changes in heart rate, MPAP, pulmonary capillary wedge pressure, O_2 consumption index, O_2 extraction ratio, and intrapulmonary shunt fraction (Tables 3 and 4). Twenty minutes after drug discontinuation, MAP remained less than baseline values in the nicardipine group, whereas MAP reached baseline values in the nitroprusside group. At this time, SVRI remained lower and CI higher than baseline values in both groups, but MAP and oxygen extraction ratio were less in the nicardipine group than in the nitroprusside group. The MAP reached its baseline value in a mean time of 43 min after nicardipine discontinuation (range 27–88 min). Twenty minutes after nitroprusside discontinuation, right atrial pressure increased significantly. An increase in MAP, MPAP, CI, O_2 consumption index, and arteriovenous difference in O_2 contents was observed in both groups 80 min after drug discontinuation. The SVRI remained lower than baseline values in the nicardipine group, and MAP and SVRI were lower in this group than in the nitroprusside group at this final measurement.

In one patient, induction of hypotension with nitroprusside resulted in too large a decrease in arterial blood pressure, associated with decreases in MPAP, pulmonary capillary wedge pressure, CI, and $S\bar{v}O_2$ <50%. These variables were corrected by administering polygeline. No episodes of $S\bar{v}O_2$ <50% attributable to the hypotension technique were recorded in the nicardipine group. No changes in electrocardiographic recording were observed in either group. Apparently, no patients suffered from short- or long-term adverse effects due to hypotension. All wake-up tests were normal. There was no clinically evident central or spinal nervous system impairment in any of our patients.

Plasma nicardipine concentrations decreased significantly during infusion (Figure 1). There were no differences between the measurement obtained at nicardipine discontinuation and those obtained 20 and 80 min later. No correlations were found between concentrations and hemodynamics.

Discussion

The effectiveness of inducing deliberate hypotension to reduce blood loss and improve visibility in the operative field during spinal surgery for scoliosis is well established (10,11). This technique, coupled with autotransfusion, can eliminate the need for homologous blood transfusion with its attendant concerns

Table 2. Infusion Rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$) of Nitroprusside and Nicardipine During and at the End of Administration

	During infusion			
Study group	20 min	80 min	140 min	Infusion end
SNP	4.1 ± 0.9	4.0 ± 0.85	3.9 ± 0.8	3.0 ± 0.8
NIC	0.93 ± 0.07	0.91 ± 0.07	0.83 ± 0.06	0.53 ± 0.13[a]

SNP, nitroprusside; NIC, nicardipine.
Results are expressed as mean ± SEM.
$P < 0.05$ versus data at 20 min.

Table 3. Hemodynamic Variables Before, During, and After Nitroprusside and Nicardipine Administration

	Study group	Before infusion	During infusion			Infusion end	After infusion	
			20 min	80 min	140 min		20 min	80 min
MAP (mm Hg)	SNP	79 ± 3	57 ± 1[a]	56 ± 1[a]	55 ± 1[a]	57 ± 1[a]	73 ± 4	96 ± 5[a]
	NIC	68 ± 1	59 ± 1[a]	58 ± 1[a]	55 ± 2[a]	57 ± 2[a]	60 ± 2[a,b]	79 ± 4[a,b]
HR (beats/min)	SNP	85 ± 7	89 ± 8	95 ± 7	91 ± 7	91 ± 7	89 ± 7	93 ± 7
	NIC	71 ± 3	83 ± 6	77 ± 3	80 ± 5	82 ± 5	83 ± 5	90 ± 7
CI ($L \cdot min^{-1} \cdot m^{-2}$)	SNP	2.7 ± 0.1	3.6 ± 0.2[a]	3.6 ± 0.3[a]	3.6 ± 0.2[a]	3.2 ± 0.2[a]	3.0 ± 0.1[a]	3.6 ± 0.2[a]
	NIC	2.5 ± 0.1	3.6 ± 0.3[a]	3.6 ± 0.2[a]	3.4 ± 0.1[a]	3.4 ± 0.3[a]	3.5 ± 0.3[a]	4.1 ± 0.3[a]
RAP (mm Hg)	SNP	4 ± 1	4 ± 1	4 ± 1	5 ± 1	5 ± 1	7 ± 1[a]	5 ± 1
	NIC	3 ± 1	4 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1	4 ± 1
MPAP (mm Hg)	SNP	13 ± 1	12 ± 1	12 ± 1	12 ± 1	13 ± 1	15 ± 1	17 ± 2[a]
	NIC	12 ± 1	14 ± 1	12 ± 1	12 ± 1	13 ± 1	13 ± 1	16 ± 1[a]
PCWP (mm Hg)	SNP	5 ± 1	5 ± 1	5 ± 1	6 ± 1	5 ± 1	7 ± 1	5 ± 1
	NIC	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^2$)	SNP	2247 ± 109	1214 ± 64[a]	1191 ± 95[a]	1188 ± 90[a]	1360 ± 87[a]	1801 ± 99[a]	2031 ± 83
	NIC	2136 ± 118	1308 ± 126[a]	1260 ± 81[a]	1249 ± 73[a]	1352 ± 131[a]	1370 ± 94[a]	1518 ± 108[a,b]
PVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^2$)	SNP	229 ± 21	164 ± 14[a]	160 ± 17[a]	152 ± 14[a]	185 ± 14	243 ± 18	268 ± 37
	NIC	231 ± 16	195 ± 22[a]	178 ± 24[a]	176 ± 14[a]	202 ± 14	197 ± 17	226 ± 19

MAP, mean arterial blood pressure; HR, heart rate; CI, cardiac index; RAP, right atrial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; NIC, nicardipine; SNP, nitroprusside.
Results are expressed as mean ± SEM.
[a] $P < 0.05$ versus before infusion.
[b] $P < 0.05$ versus nitroprusside.

(12). Most often, hypotension is induced by a potent vasoactive agent with predictable, short-lived, and easily reversible effects. For these reasons, sodium nitroprusside remains very desirable, although there is a risk of cyanide poisoning at doses >1.5 mg/kg (13). This randomized study indicates that nicardipine and nitroprusside can be administered to result in similar operative conditions. Blood loss and the amount of blood cells and polygeline required to maintain hematocrit within the 26%–30% range were similar in both groups. Onset of hypotension was similar. Desired levels of arterial blood pressure were easily maintained without deleterious effects on global O_2 delivery (as indicated by $S\bar{v}O_2$), except for one patient in the nitroprusside group. However, the results obtained with both nitroprusside and nicardipine should be interpreted in light of several factors.

Although we do not exclude possible changes because of small sample size, no tachycardia and no deterioration in arterial oxygenation were observed in either group, contrary to the effects usually observed with nitroprusside (14) and dihydropyridine calcium channel blockers (15,16). The hypotension produced by both nitroprusside and nicardipine is due to their direct vasodilatory properties. Resulting baroreflex stimulation then leads to a compensatory increase in sympathetic tone (17,18). Seagard et al. (19) have demonstrated that isoflurane blocks canine baroreflex pathways both peripherally and centrally. Nitrous oxide, morphine, and diazepam can also produce this depression (20). Thus, in our study, the anesthetic depression of baroreflex function may have played an important role in the reduction of nicardipine- and nitroprusside-induced cardiac and vascular stimulation. In the presence of isoflurane-N_2O, sympathetic-mediated increases in cardiac output and peripheral vascular tone did not modulate the direct vasodilation produced by both nicardipine and nitroprusside. Finally, we believe that the decrease in MAP was magnified by isoflurane-N_2O anesthesia, and we agree with Bedford (21,22) that part of the well-

Table 4. Metabolic Variables Before, During, and After Nitroprusside and Nicardipine Administration

	Study group	Before infusion	During infusion			Infusion end	After infusion	
			20 min	80 min	140 min		20 min	80 min
$\dot{V}o_2$ (mL $O_2 \cdot min^{-1} \cdot m^{-2}$)	SNP	87 ± 3	99 ± 6	101 ± 7	94 ± 7	101 ± 11	115 ± 12	179 ± 28[a]
	NIC	94 ± 5	100 ± 6	102 ± 8	99 ± 5	116 ± 14	114 ± 15	178 ± 15[a]
OER	SNP	0.20 ± 0.01	0.20 ± 0.01	0.22 ± 0.01	0.23 ± 0.02	0.25 ± 0.01	0.28 ± 0.02[a]	0.32 ± 0.03[a]
	NIC	0.24 ± 0.02	0.19 ± 0.02	0.21 ± 0.01	0.23 ± 0.01	0.24 ± 0.02	0.23 ± 0.02[b]	0.30 ± 0.03
$C(a - \bar{v})O_2$ (mL O_2/dL)	SNP	3.3 ± 0.2	2.8 ± 0.1[a]	2.8 ± 0.1[a]	2.7 ± 0.2[a]	3.2 ± 0.3	3.8 ± 0.4	4.8 ± 0.5[a]
	NIC	3.7 ± 0.3	2.8 ± 0.3[a]	2.9 ± 0.3[a]	2.9 ± 0.2[a]	3.4 ± 0.3	3.3 ± 0.4	4.6 ± 0.5[a]
$\dot{Q}_s/\dot{Q}_t$	SNP	0.12 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.09 ± 0.01
	NIC	0.12 ± 0.02	0.10 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.11 ± 0.02	0.13 ± 0.02	0.11 ± 0.02
pHa	SNP	7.46 ± 0.13	7.44 ± 0.13	7.43 ± 0.15	7.43 ± 0.15	7.40 ± 0.18[a]	7.41 ± 0.16[a]	7.39 ± 0.14[a]
	NIC	7.47 ± 0.16	7.43 ± 0.14	7.44 ± 0.14	7.44 ± 0.10	7.39 ± 0.10[a]	7.37 ± 0.18[a]	7.50 ± 0.18[a]
$Paco_2$ (kPa)	SNP	4.40 ± 0.19	4.47 ± 0.19	4.64 ± 0.17	4.62 ± 0.14	4.89 ± 0.19[a]	4.81 ± 0.24[a]	5.01 ± 0.24[a]
	NIC	4.56 ± 0.20	5.05 ± 0.19	4.75 ± 0.17	4.65 ± 0.15	4.99 ± 0.18[a]	5.26 ± 0.16[a]	5.21 ± 0.20[a]
Hb (g/dL)	SNP	11.6 ± 0.6	10.2 ± 0.6[a]	9.3 ± 0.7[a]	8.6 ± 0.6[a]	9.2 ± 0.7[a]	9.6 ± 0.6[a]	10.7 ± 0.4[a]
	NIC	11.6 ± 0.7	11.0 ± 0.6[a]	9.9 ± 0.6[a]	9.3 ± 0.6[a]	10.0 ± 0.3[a]	10.4 ± 0.6[a]	10.9 ± 0.6[a]
Protein (g/L)	SNP	61 ± 1	57 ± 2	51 ± 2[a]	47 ± 2[a]	44 ± 2[a]	45 ± 2[a]	47 ± 2[a]
	NIC	61 ± 1	54 ± 1	51 ± 2[a]	46 ± 2[a]	46 ± 3[a]	47 ± 3[a]	45 ± 2[a]

$\dot{V}o_2$, oxygen consumption index; OER, oxygen extraction ratio; $C(a - \bar{v})o_2$, arteriovenous difference in O_2 contents; $\dot{Q}_s/\dot{Q}_t$, intrapulmonary shunt fraction; pHa, arterial pH; $PaCO_2$, arterial CO_2 tension; Hb, hemoglobin; Protein, protein concentration; NIC, nicardipine; SNP, nitroprusside.
Results are expressed as mean ± SEM.
[a] $P < 0.05$ versus before infusion.
[b] $P < 0.05$ versus nitroprusside.

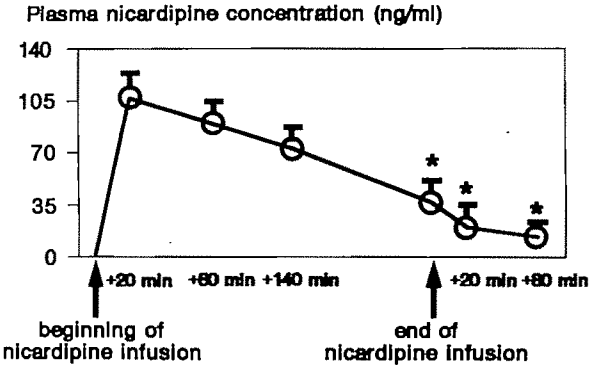


Figure 1. Changes in plasma nicardipine concentration. Results are mean ± SEM. *$P < 0.05$ data at the end of nicardipine administration and 20 and 80 min after discontinuation versus data at 20, 80, and 140 min during nicardipine administration.

known disadvantages of nitroprusside, including reflex tachycardia, tachyphylaxis, and rebound hypertension, may have been reduced by anesthesia.

Hemodilution may have also influenced the outcome of our study. Vasodilation may in part be attributed to rheologic changes induced by hemodilution (23), as indicated by decreased vascular resistance 20 min after nitroprusside discontinuation. Further, in normal lung tissue, except during chronic ventilation-perfusion maldistribution (24), vasodilators increase intrapulmonary shunt fraction by increasing blood flow to the lung areas, where nonventilated alveoli are located. In scoliosis, the number of vascular units per lung area is less than that in normal lung (25), and in regions compressed by the rib cage deformity, alveoli approach their closing volume (26). Thus, given the relatively high value of the shunt fraction before hypotension in our study, it is possible that pulmonary vasodilation did not result in further recruitment of lung vessels.

The time-course of plasma nicardipine concentration provides further evidence that the anesthetic pattern had an influence on the vasodilator hemodynamic and pharmacokinetic variables in our study. A mean dose of 6.2 mg of nicardipine was required to achieve the desired level of hypotension in a mean time of 11 min. At the first determination (approximately 10 min after the end of our initial infusion), (Figure 1) this dose resulted in a plasma concentration >100 ng/mL. This value was twice those previously published (27,28) for awake patients using a protocol of doses and timing that were approximately equal to those used in the current study. Seki and Takenaka (27), in healthy patients, and Slike et al. (28), in patients with coronary artery disease, administered nicardipine (5–10 mg IV) for 5 min. They found that plasma nicardipine concentrations were <50 ng/mL at 10 min after the end of infusion. Our results also differ from those obtained in patients with hypertension who received a mean dose of 13 mg of nicardipine (i.e., twice our initial dose), resulting in a mean plasma concentration of 80 ng/mL (29). In this latter group, clinical cessation of action associated with a plasma nicardipine concentration of 32.5 ± 4.1 ng/mL (mean ± SD) was obtained 17 min after discontinuation of a 6-h maintenance infusion of 3 mg/h. Based on laboratory data that demonstrate

that volatile anesthetics may interfere with calcium channel blocker disposition and lead to increased plasma concentration and decreased systemic clearance (3,30), we believe that the discrepancy between these previous results and ours may be attributable to isoflurane.

Nicardipine is a lipid-soluble basic molecule (pKa 7.2) that at physiologic pH is highly bound (>90%) to plasma proteins (31). Its terminal elimination half-life is 1.2–1.4 h after intravenous administration of 5–15 mg (32). Experimental evidence supports the belief that the pharmacodynamic properties of nicardipine, like most calcium channel blockers (33–35), are plasma drug-concentration related in awake and anesthetized dogs, even though isoflurane anesthesia alters this concentration-effect relationship (3). In the presence of isoflurane, the slopes of these linear relationships are reduced for most hemodynamic variables (3). Results obtained in humans confirm that plasma nicardipine levels are correlated to arterial blood pressure changes (36,37), even if continuous intravenous administration is prolonged over 48 h (38).

However, decreased plasma nicardipine concentrations were accompanied in our study by unchanged arterial blood pressure. Conversely, after discontinuation of infusion, the return to normal arterial blood pressures was associated with unchanged plasma nicardipine concentrations. Therefore, we failed to find any plasma concentration-effect relationship. The fact that arterial blood pressure remained low with decreasing plasma levels of nicardipine suggests that a counterclockwise hysteresis occurred after prolonged continuous administration of nicardipine. This may be an indication of an increasing effect over time for the same concentration of drug. Previously, hysteresis was noted with other calcium channel blockers (39,40) and was attributed to the formation of active metabolites or a delay before equilibrium between plasma concentrations and concentrations at the receptors is reached. Nicardipine undergoes extensive hepatic metabolism, including *N*-dealkylation, *N*-demethylation, and oxidative deamination. The pharmacologic activity of the metabolites is 1/100 that of nicardipine (32). Thus, hysteresis due to active metabolites of nicardipine appears unlikely. It is possible that progressive decreased plasma protein concentration due to hemodilution resulted in a higher free fraction of nicardipine and that equilibrium of drug concentrations between plasma and site of action was modified, inducing a more marked hypotensive effect than expected. However, unaltered protein binding has been demonstrated with nicardipine, even in cases of low plasma protein concentration (41). Finally, the reason for this hysteresis is not known but may be due to the release of other vasodilating mediators. As suggested by the progressive decreased pH, a prolonged surgical hypotensive state may have led to relative tissue hypoperfusion.

To conclude, our results establish that prolonged administration of nicardipine induced deliberate hypotension during scoliosis surgery. Although no cumulative nicardipine levels were found in the plasma, nicardipine resulted in a prolonged hypotensive state. Clinicians should be prepared for this eventuality if they choose to use nicardipine. Newer calcium channel blockers may have more favorable pharmacokinetics and prove more suitable for deliberate hypotension.

We thank M. Cadio, RN, M. A. Rimbert, RN, and F. Bréard, RN, for technical assistance, and D. David, MD, I. Bourdeix, and the Sandoz Laboratory, Rueil, Malmaison, France, for supplying nicardipine and providing plasma nicardipine determinations.

References

1. Bernard J-M, Pinaud M, François T, Macquin-Mavier I, Letenneur J. Deliberate hypotension with nicardipine or nitroprusside during total hip arthroplasty. Anesth Analg 1991;73:341–5.
2. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
3. Chelly JE, Hysing ES, Abernethy DR, et al. Role of isoflurane on hemodynamic properties and disposition of nicardipine. J Pharmacol Exp Ther 1987;241:899–906.
4. Hysing ES, Chelly JE, Doursout M-F, Hartley C, Merin RG: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. III. Nicardipine and isoflurane. Anesthesiology 1986;65: 385–91.
5. Atlee JL III, Hamann SR, Brownlee SW, Kreigh C. Conscious state comparisons of the effects of the inhalation anesthetics and diltiazem, nifedipine, or verapamil on specialized atrioventricular conduction times in spontaneously beating dog hearts. Anesthesiology 1988;68:519–28.
6. Lambert CR, Hill JA, Nichols WN, Feldman RL, Pepine CJ. Coronary and systemic hemodynamic effects of nicardipine. Am J Cardiol 1985;55:652–6.
7. Watary N, Mizumura J, Higuchi S. Simultaneous microdetermination of nicardipine and its pyridine metabolite in body fluids by capillary column gas chromatography with electron-capture detection. J Chromatogr 1990;530:438–46.
8. Stanley TE, Reves JG. Cardiovascular monitoring. In: RD Miller, ed. Anesthesia. 3rd ed. New York: Churchill Livingstone, 1990:1031–99.
9. Moon RE, Camporesi EM. Respiratory monitoring. In: RD Miller, ed. Anesthesia. 3rd ed. New York: Churchill Livingstone, 1990:1129–62.
10. Malcolm-Smith NA, MacMaster MJ. The use of induced hypotension to control bleeding during posterior fusion for scoliosis. J Bone Joint Surg (Br) 1983;65:255–8.
11. Patel NJ, Patel BS, Paskine S, Laufer S. Induced moderate hypotensive anesthesia for spinal fusion and Harrington-rod instrumentation. J Bone Joint Surg (Am) 1985;67:1384–7.
12. Mandel RJ, Brown MD, McColough NC, Pallares V, Varlotta R. Hypotensive anesthesia and autotransfusion in spinal surgery. Clin Orthop 1981;154:27–33.

13. Michenfelder JD, Tinker JH. Cyanide toxicity and thiosulfate protection during chronic administration of sodium nitroprusside in the dog: correlation with a human case. Anesthesiology 1977;47:441–8.
14. Golberg ME, McNulty SE, Azad SS, et al. A comparison of labetolol and nitroprusside for inducing hypotension during major surgery. Anesth Analg 1990;70:537–42.
15. Rousseau MF, Vincent MF, Van Hoof F, Van den Berghe G, Charlier AA, Pouleur H. Effects of nicardipine and nisoldipine on myocardial metabolism, coronary blood flow and oxygen supply in angina pectoris. Am J Cardiol 1984;54:1189–94.
16. Casthely PA, Villanueva R, Rabinowitz L, Gandhi P, Litwak B, Fynman PN. Intrapulmonary shunting during deliberate hypotension with nifedipine, diltiazem and labetolol in dogs. Can Anaesth Soc J 1985;32:119–23.
17. Knight PP, Lane GA, Heninger RN, Bolles RS, Bjoraker DJ. Catecholamine and renin angiotensin response during hypotensive anesthesia induced by sodium nitroprusside or trimetaphan camsylate. Anesthesiology 1983;59:248–53.
18. Waltier DC, Zyvoloski MG, Gross GJ, Brooks HL. Comparative actions of dihydroperidine slow calcium channel blocking agents in conscious dogs: alterations in baroreflex sensitivity. J Pharmacol Exp Ther 1984;230:376–82.
19. Seagard JL, Elegbe EO, Hopp FA, et al. Effects of isoflurane on the baroreceptor reflex. Anesthesiology 1983;59:511–20.
20. Kortly KJ, Ebert TJ, Vucin EJ. Baroreceptor reflex control of heart during morphine sulfate, diazepam, N_2O/O_2 anesthesia in humans. Anesthesiology 1984;558–63.
21. Bedford RF. Increasing halothane concentrations reduce nitroprusside dose requirement. Anesth Analg 1978;57:457–62.
22. Bedford RF. Sodium nitroprusside: hemodynamic dose-response during enflurane and morphine anesthesia. Anesth Analg 1979;58:174–8.
23. Crystal JG, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. Anesth Analg 1988;67:211–8.
24. Casthely PA, Lear S, Cottrel J, Lear E. Intrapulmonary shunting during induced hypotension. Anesth Analg 1982;61:231–5.
25. Davies G, Reid L. Effect of scoliosis on growth of alveoli and pulmonary arteries and on the right ventricle. Arch Dis Child 1971;46:623–32.
26. Turino GM, Goldring RM, Fishman AP. Cor pulmonale in musculoskeletal abnormalities of the thorax. Bull NY Acad Med 1985;41:959–80.
27. Seki T, Takenaka T. Pharmacological evaluation of YC-93, a new vasodilator, in healthy volunteers. Int J Clin Pharmacol Res 1977;15:267–74.
28. Slike B, Verma SP, Frais MA, Reynolds G, Jackson N, Taylor SH. Haemodynamic analysis of the effects of nicardipine and metoprolol alone and in combination in coronary artery disease. Eur Heart J 1985;6:930–8.
29. The IV Nicardipine Study Group. Efficacy and safety of intravenous nicardipine in the control of postoperative hypertension. Chest 1991;99:393–8.
30. Rogers K, Hysing ES, Merin RG, Taylor A, Hartley C, Chelly JE. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetic in chronically instrumented dogs. II. Verapamil, enflurane, and isoflurane. Anesthesiology 1986;64:568–75.
31. Higuchi S, Shiobara Y. Metabolic rate of nicardipine hydrochloride, a new vasodilator, by various species in vitro. Xenobiotica 1980;10:889–96.
32. Turlapaty P, Vary R, Kaplan JA. Nicardipine, a new intravenous calcium antagonist: a review of its pharmacology, pharmacokinetics, and perioperative applications. J Cardiothorac Anesth 1989;3:344–55.
33. Browne RK, Dimmit DC, Miller LD, Korol B. Relationship between plasma diltiazem and cardiovascular responses in conscious dogs. J Cardiovasc Pharmacol 1983;5:483–90.
34. McAllister RG, Bourne DW, Dittert LW. The pharmacology of verapamil. I. Elimination kinetics in dog and correlation of plasma levels with effect on the electrocardiogram. J Pharmacol Exp Ther 1977;202:38–44.
35. Hamann SR, Kaltenborn KE, McAllister RG. Pharmacodynamic comparison of verapamil and nifedipine in anesthetized dogs. J Cardiovasc Pharmacol 1985;7:224–34.
36. Razack TA, McNeil JJ, Sewell RB, et al. The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. Clin Pharmacol Ther 1990;47:463–9.
37. Porchet HC, Dayer P. Serum concentrations and effects of (±)-nicardipine compared with nifedipine in a population of healthy subjects. Clin Pharmacol Ther 1990;48:155–60.
38. Cook E, Clifton GG, Vargas R, et al. Pharmacokinetics, pharmacodynamics, and minimum effective clinical dose of intravenous nicardipine. Clin Pharmacol Ther 1990;47:706–18.
39. Ellenbogen KA, Roark SF, Smith MS, McCarthy EA, Bjornsson TD, Pritchett ELC. Effects of sustained intravenous diltiazem infusion in healthy persons. Am J Cardiol 1986;58:1055–60.
40. Joyal M, Pieper J, Cremer K, Feldman RL, Pepine CJ. Pharmacodynamic aspects of intravenous diltiazem administration. Am Heart J 1986;111:54–61.
41. Urien S, Albengres E, Comte A, Kiechel JR, Tillement JP. Plasma protein binding and erythrocyte partioning of nicardipine in vitro. J Cardiovasc Pharmacol 1985;7:891–8.

Effects of Hypocarbia on the Pharmacodynamics of Sufentanil in Humans

Richard S. Matteo, MD, Eugene Ornstein, PhD, MD, Arthur E. Schwartz, MD, William L. Young, MD, Jeffrey Weinstein, MD, and Charles F. Cain, MD

Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, and the Anesthesiology Service, Presbyterian Hospital, New York, New York

Descriptors of power and frequency derived from power spectral analysis of the electroencephalogram (EEG) were used to determine the effects of low-dose sufentanil (0.1 μg/kg) on brain activity. The effects of hypocarbia alone and of hypocarbia with sufentanil in patients receiving a N_2/O_2 (70%:30%) anesthetic were also studied. Hypocarbia alone caused changes in most EEG descriptors from both the anterior (F_3–C_3) and posterior (P_3–O_1) EEG montages. All EEG descriptors in both hypocarbic and normocarbic patients significantly changed when sufentanil was administered, reflecting a shift of power into the lower frequency ranges. When the anterior EEG montages from the two groups that received sufentanil were compared, the delta power band, spectral edge 50 (median power frequency), and the relative power in the delta power band divided by the alpha plus beta power bands [D/(A + B)] in the hypocarbic group exhibited a significantly greater shift of power into the lower frequency range. It is concluded that (a) power spectral analysis is a sensitive measure of the effects of hypocarbia and small doses of sufentanil on the brain; (b) the power spectral analysis descriptors—delta power band, spectral edge 50, and [D/(A + B)]—are statistically the most sensitive to EEG changes induced by sufentanil; and (c) hypocarbia intensifies patient EEG response to sufentanil, as judged by changes in EEG descriptors.

(Anesth Analg 1992;75:186–92)

Hypocarbia alters the distribution and elimination of narcotics in animals. Nishitateno et al. (1) reported that hypocarbia in dogs decreased plasma clearance of morphine while increasing brain concentration of morphine. In a similar study, Ainslie et al. (2) found the same results in dogs that were given fentanyl. In humans given fentanyl, Cartwright et al. (3) reported that hyperventilation caused a decreased plasma clearance of the drug and a prolonged respiratory depression. Most recently, Schwartz et al. (4) demonstrated that induced hypocarbia in humans prolonged the elimination of sufentanil.

This study was undertaken to determine if hypocarbia altered the action of sufentanil on the brain in humans. Power spectral analysis (PSA) of the electroencephalogram (EEG) was used to study these effects.

Accepted for publication March 31, 1992.

Address correspondence to Dr. Matteo, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, NY 10032.

Methods

After institutional approval, informed consent was obtained from 36 patients, ranging in age from 19 to 62 yr, who were to have surgery of the lumbar or thoracic spine. These patients were divided into four groups: group 1, normocarbia without narcotic (n = 6); group 2, hypocarbia without narcotic (n = 6); group 3, normocarbia with sufentanil (n = 12); group 4, hypocarbia with sufentanil (n = 12). All patients were ASA physical status I or II and had no hepatic or renal disease. None had received narcotics for 1 wk before the study. Premedication consisted of glycopyrrolate (0.2 mg IM) 45–60 min before induction of anesthesia. Intravenous and radial artery lines were placed before induction of anesthesia, and routine monitoring was performed. The EEG leads were placed in the F_3–C_3 and P_3–O_1 positions. The data collection system consists of a modified PSA device (Neurotrac, Interspec, Ambler, Pa.) that digitizes the EEG signals and performs a fast Fourier transformation and transfers this data in 2-s epochs to a Macintosh computer where it is stored on a hard disk for further processing. The raw analogue EEG was acquired with a high-pass filter of 30 Hz (−3 dB at

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

30 Hz; 60 dB/decade) and a single-pole low-pass filter of 1 Hz (−3 dB at 1 Hz; 20 dB/decade). In addition, the two channels of analogue EEG data, along with an audio channel for recording anesthetic or surgical events, were recorded with a Vetter model C-8 FM tape recorder (A. R. Vetter Co., Rebersburg, Pa.).

Anesthesia was induced with an intravenous bolus dose of thiopental (4 mg/kg) followed by succinylcholine (1 mg/kg) and tracheal intubation. Anesthesia was maintained with N_2O/O_2 (70%:30%), and paralysis was provided with vecuronium. Once a steady-state EEG pattern was observed, usually appearing as theta waves with superimposed fast activity (5,6) or occasionally low-voltage fast activity (7), the study was begun. This point was reached 25–30 min after the administration of thiopental and after placement of the patient in the prone position.

In all groups when steady-state ventilation was achieved, analysis of arterial blood gases was performed. In group 1 (normocarbia), the end-tidal CO_2 ($ETco_2$) was adjusted between 35 and 38 mm Hg and data was collected for 10–15 minutes. In group 2, normocarbia was achieved as in group 1, and after 5 min of data collection the ventilation was increased to achieve an $ETco_2$ of 20–24 mm Hg. The steady-state hypocarbic EEG was compared with the normocarbic state to determine the effects of hypocarbia alone on the EEG. In group 3, steady-state normocarbia was achieved, and at this point sufentanil (0.1 μg/kg) was given as a bolus dose, the initial normocarbic state being taken as control. In group 4, steady-state hypocarbia was achieved ($ETco_2$ 20–24 mm Hg), and sufentanil (0.1 μg/kg) was administered as in group 3, the initial hypocarbic state being taken as control. Based on the observation that all EEG descriptors reached their maximal value 232–352 s after injection, the value of the descriptors 5 min after the injection of sufentanil was taken as the maximum response. These values were then compared with the baseline values. The studies were terminated before the start of surgery.

The fast Fourier transform data stored in the computer were then further processed to derive 29 descriptors of power and frequency. Among these were total power (TP); multiple spectral edges (SE) between 50% and 97%; peak power frequency (PPF); relative power in various frequency bands—delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–13 Hz), beta (13 Hz and up), and three intermediate bands that overlapped the four standard bands; and percent power in each of the seven previous frequency bands. Six additional descriptors were the value of the descriptors from combinations of the seven previous frequency bands that were designed to emphasize the expected narcotic-induced shift of power from the higher frequencies into the lower frequency bands. Preliminary examination of these 29 descriptors revealed that data from the three intermediate power bands and percent power in all seven frequency bands provided no additional information over relative power in the standard power bands. Of the six derived descriptors, relative power in delta divided by alpha plus beta [D/(A + B)] and relative power in delta plus theta divided by alpha plus beta [(D + T)/(A + B)] provided the most information. Thus, only 15 descriptors were used in the final data analysis. These descriptors were total power (TP); relative power in the delta power band (D); relative power in the theta power band (T); relative power in the alpha power band (A); relative power in the beta power band (B); PPF; spectral edges 50–97 (SE50, SE60, SE70, SE80, SE90, SE95, SE97); relative power in the delta power band divided by the alpha plus beta power bands [D/(A + B)]; and relative power in the delta and theta power bands divided by the alpha and beta power bands [(D + T)/(A + B)].

These data were then transformed by taking the baseline (initial steady state) value for each descriptor as 100 (Transformed descriptor = 100 × Absolute value/Absolute baseline value). Because the absolute value of the various descriptors varied greatly from patient to patient, transformation of the data permitted comparison of the data between individual patients and groups of patients. In preparing the data for analysis, 15 sequential 2-s epochs for each descriptor were averaged (30-s time periods). Finally, the transformed data were presented graphically in terms of percent change from the baseline. To determine onset time of narcotic action and time to maximum effect, descriptors from 2-s epochs were plotted sequentially. The significance of alteration of transformed EEG descriptors in individual patients within groups resulting from hypocarbia or narcotic injection was determined by applying Student's *t*-test for paired data (two-tailed). When two groups were compared one with the other, or when times of onset and times of maximum effect were estimated, Student's *t*-test for unpaired data (two-tailed) was used. Gender ratios were compared with the χ^2-test; $P < 0.05$ was considered significant for all comparisons.

Results

The demographic characteristics of the groups and the intraoperative conditions are summarized in Table 1. There is no significant difference among the four groups as to age, gender ratio, weight, and body temperature. The $ETco_2$ and arterial CO_2 tension ($Paco_2$) of the two normocarbic groups (1,3) and hypocarbic groups (2,4) did not vary significantly. As expected, the $ETco_2$ and $Paco_2$ in the two hypocarbic

Table 1. Patient Demographics and Intraoperative Conditions in the Four Study Groups

	Normocarbia only (n = 6)	Hypocarbia only (n = 6)	Normocarbia + sufentanil (n = 12)	Hypocarbia + sufentanil (n = 12)
Age (yr)	43.8 ± 13	44.5 ± 16	50.3 ± 13	41.1 ± 11
Weight (kg)	88.0 ± 18	79.5 ± 11	74.0 ± 18	80.4 ± 14
Gender (F/M)	2/4	2/4	4/8	3/9
$ETco_2$ (mm Hg)	34.5 ± 2	20.0 ± 0.7	34.9 ± 2	20.5 ± 1
$Paco_2$ (mm Hg)	38.8 ± 1	24.1 ± 3	40.8 ± 3	24.9 ± 2
Temperature (°C)	35.1 ± 0.5	35.7 ± 0.5	35.5 ± 0.5	35.6 ± 0.4

F, female; M, male; $ETco_2$, end-tidal CO_2 tension; $Paco_2$, arterial CO_2 tension.
Values are given as mean ± SD.

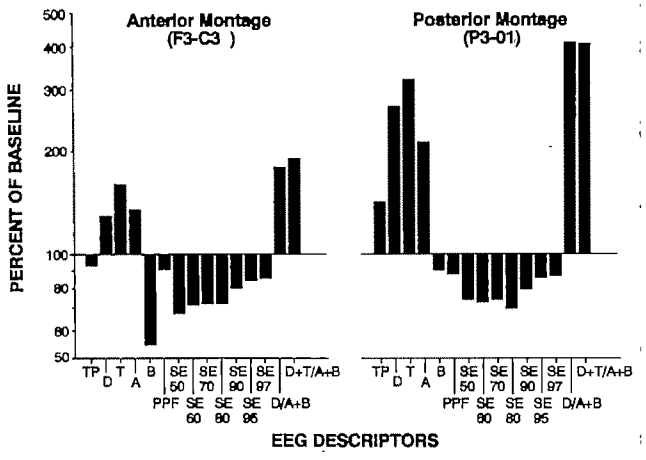


Figure 1. Effects of hypocarbia alone on EEG descriptors. *Bar lines*, mean percent change from the transformed baseline. Both the anterior (F_3–C_3) and posterior (P_3–O_1) EEG montages are presented. TP, total power; D, delta power band; T, theta power band; A, alpha power band; B, beta power band; PPF, peak power frequency; SE50–SE97, spectral edges 50%–97%; D/A + B, delta power band/alpha + beta power bands; D + T/A + B, delta + theta power bands/alpha + beta power bands.

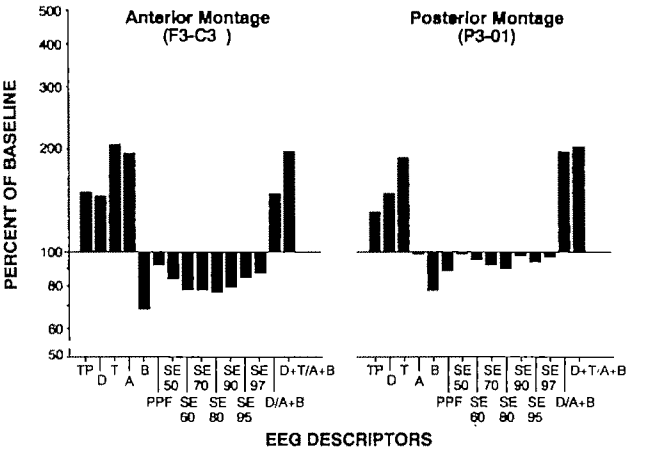


Figure 2. Effects of normocarbia plus sufentanil (0.1 μg/kg) on EEG descriptors. *Bar lines*, percent change from the transformed baseline. Both anterior (F_3–C_3) and posterior (P_3–O_1) EEG montages are presented. See Figure 1 for explanation of abbreviations.

groups were significantly less than the normocarbic groups.

The normocarbic patients (group 1) achieved a steady EEG state 15–20 min after induction of anesthesia, and the EEG descriptors derived at 2-s intervals did not vary more than ±20% subsequently. When fifteen 2-s epochs were averaged (30 s), variation decreased to ±10%. In the other three groups, hypocarbia alone or the injection of sufentanil in either normo- or hypocarbic patients caused a statistically significant alteration in all of the descriptors in both the anterior (F_3–C_3) and posterior EEG montage (P_3–O_1). The changes in descriptors in the posterior montage generally followed that of the anterior montage. Data are presented from both anterior and posterior montages (Figures 1–3).

Hypocarbia alone in the anterior montage (Figure 1) produced a shift of power into lower frequency bands with the greatest increase in the theta band, although total power (TP) was slightly decreased. The PPF and the spectral edges from 50% to 97% were all decreased. A derived descriptor [(D + T)/(A + B)] designed to emphasize power shifts into the lower frequencies showed the greatest increase (90%). In group 3 (normocarbia) (Figure 2) and group 4 (hypocarbia) (Figure 3), the intravenous administration of sufentanil also caused an increase in power in the lower frequency bands. The PPF and the spectral edges, with the exception of the PPF in the posterior montage of the hypocarbia-sufentanil group (Figure 3), were significantly decreased, whereas D/(A + B) and (D + T)/(A + B) were increased, reflecting a shift of power into the lower frequency ranges.

In comparing descriptors from the posterior with the anterior montage, a few of the descriptors in the various treatment groups moved in opposite directions. In patients subjected to hypocarbia alone (Figure 1), total power in the anterior montage decreased, whereas in the posterior montage it was increased. In

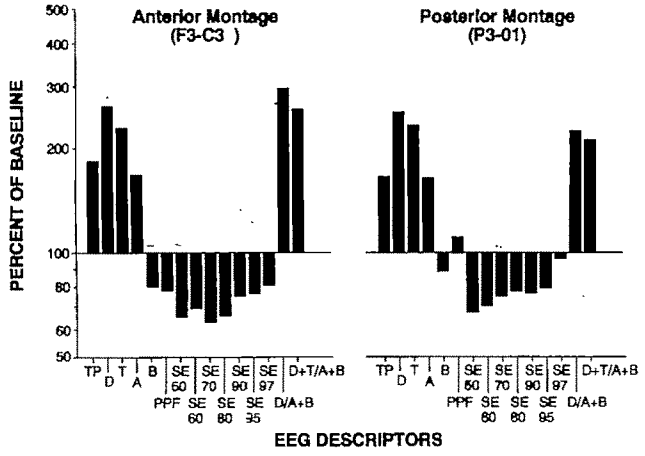


Figure 3. Effects of hypocarbia plus sufentanil (0.1 μg/kg) on EEG descriptors. *Bar lines*, percent change from the transformed baseline. Both the anterior (F_3–C_3) and posterior (P_3–O_1) EEG montages are presented. See Figure 1 for explanation of abbreviations.

normocarbic patients given sufentanil (Figure 2), alpha power was increased in the anterior montage and was unchanged in the posterior montage. In hypocarbic patients given only sufentanil (Figure 3), only one descriptor differed in direction from baseline between the anterior and posterior montages. This was the PPF, which was decreased in the anterior and increased in the posterior montage. Further, when comparing the anterior and posterior montages, the delta and theta power bins, the two derived descriptors [D/(A + B) and (D + T)/(A + B)] and the spectral edges moved in the same direction in relation to their baselines.

When the two groups of patients who received sufentanil (groups 3 and 4) were compared, three descriptors in their anterior montages showed significant differences (Table 2). The hypocarbic group of patients showed increased response in the delta power band and D/(A + B) and a decrease in the spectral edge 50 (mean power frequency) compared with the normocarbic group of patients.

In examining the data before transformation, it was found that in the normocarbic patients without narcotic, the spectral edge 50 ranged between 8 and 22 Hz, whereas their spectral edge 97 ranged between 23.5 and 29.5 Hz. In those patients who were hypocarbic, the spectral edge 50 ranged between 7 and 14.5 Hz, and their respective spectral edge 97 values ranged between 17 and 26.5 Hz.

Mean onset times after the injection of sufentanil ranged between 18 and 51 s for the various descriptors, with the maximum change achieved between 252 and 332 s. There was no significant difference for these times between the normocarbic and hypocarbic groups.

Discussion

Two studies have demonstrated that hypocarbia increases the concentration of narcotics in the brains of dogs. Nishitateno et al. (1) injected morphine into hypocarbic dogs ($Paco_2$ 20 mm Hg) and found that the morphine concentration in the cerebral cortex of these animals was significantly increased at 15–240 min compared with normocarbic dogs. Ainslie et al. (2) studied the effects of hypocarbia ($Paco_2$ 19 mm Hg) in dogs given fentanyl. They found in these animals that brain fentanyl concentration peaked at 15–20 min and was higher than in normocarbic or hypercarbic animals.

Cartwright et al. (3) studied postoperative ventilatory depression in surgical patients given fentanyl (10 or 25 μg/kg) who were maintained at either normocarbia (38–42 mm Hg) or hypocarbia (20–25 mm Hg) during anesthesia and surgery. Using a CO_2 challenge, they found that during the first 2 h after anesthesia, CO_2 responsiveness decreased to a greater degree in those patients who were hyperventilated. In addition, the authors measured plasma fentanyl concentrations and calculated pharmacokinetic variables. They found that the patients who were hyperventilated during anesthesia had a significantly lower plasma clearance of fentanyl than those who were ventilated at normal levels, although they found no difference in either the volume of distribution or elimination half-lives between groups.

Most recently, Schwartz et al. (4), studying the effects of hyperventilation on the pharmacokinetics of sufentanil in neurosurgical patients, found that hypocarbia ($Paco_2$ 22–28 mm Hg) produced an increased volume of distribution and a prolonged elimination half-life for this narcotic.

In their discussion of the causes of this effect, Schwartz et al. (4) pointed out that sufentanil has a pKa of 8.01, and as the serum pH increases, the Henderson-Hasselbalch equation predicts that the proportion of the drug in the nonionized state will increase. As the nonionized state of sufentanil is the active form that rapidly crosses the blood-brain barrier, hyperventilation with accompanying hypocarbia might be expected to produce a more rapid onset and a more profound action of the narcotic.

The human scalp-recorded EEG was chosen as the method for measuring the actions of both hypocarbia and sufentanil because it is a noninvasive technique, and it is well established that the EEG is a very sensitive means of measuring the effects of drugs and physiologic changes on brain function. Fink (8) has, in fact, coined the term "pharmaco-EEG analysis" to describe the use of the EEG to quantitate drug action on the brain. In addition, it has been clearly demonstrated that both hypocarbia and narcotics alter EEG

Table 2. Comparison of Transformed[a] Electroencephalographic Descriptors From Normocarbic and Hypocarbic Patients Who Received Sufentanil (0.1 μg/kg IV)

Descriptors from anterior montage (F_3–C_3)	Normocarbia (mean ± SD)	Hypocarbia (mean ± SD)	*P* value
Total power	149 ± 92	182 ± 73	0.3355
Delta (0.5–3.5 Hz)	146 ± 92	263 ± 101	0.0064
Theta (3.5–7.5 Hz)	205 ± 147	228 ± 174	0.7175
Alpha (7.5–13 Hz)	192 ± 245	167 ± 136	0.7602
Beta (13 Hz and up)	68 ± 27	80 ± 51	0.4802
Peak power frequency	92 ± 24	78 ± 35	0.2729
Spectral edge 50	84 ± 17	65 ± 25	0.0421
Spectral edge 60	78 ± 12	69 ± 20	0.2229
Spectral edge 70	78 ± 19	63 ± 21	0.0871
Spectral edge 80	76 ± 21	66 ± 21	0.2223
Spectral edge 90	79 ± 25	75 ± 15	0.6253
Spectral edge 95	85 ± 23	76 ± 14	0.2816
Spectral edge 97	87 ± 21	80 ± 14	0.3519
D/(A + B)	148 ± 93	296 ± 163	0.0118
(D + T)/(A + B)	194 ± 123	258 ± 153	0.2708

Values obtained 5 min after injection.
[a]All descriptors transformed by taking baseline values as 100.

patterns of humans in a reproducible manner. As early as 1940, Gibbs et al. (9), studying the effects of hypocarbia on the EEG, reported "a shift in energy towards the slow side of the spectrum," with an apparent increase in the total amount of energy. Soon thereafter, Davis and Wallace (10) confirmed this observation. Insofar as the effects of hypocarbia during anesthesia are concerned, Geddes and Gray (11), studying hyperventilation during the maintenance of nitrous oxide, oxygen, relaxant anesthesia, were the first to report delta wave activity with hyperventilation (pH 7.5). The newer synthetic narcotics, fentanyl and its analogues sufentanil and alfentanil, have in high doses all been shown to induce *similar* EEG changes in humans (12–15). This response consists of a slowing of the EEG with increased power in the lower frequency range (delta band). A similar picture has also been reported with smaller doses of sufentanil and fentanyl (16).

Two other anesthetics were used in this study: N_2O and thiopental. The question arises, are these drugs influencing the reported EEG results? Nitrous oxide with adequate oxygen has been shown to induce EEG changes. These were reported as fast oscillatory activity with a peak frequency of 34 Hz (7), regular 5–7 Hz activity (17), loss of alpha rhythm, and appearance of theta activity with superimposed fast activity (5) when given at 1 MAC (in a pressure chamber), and slow rhythmic activity (5). Sebel et al. (18), however, reported that the EEG pattern after fentanyl injection is the same in patients ventilated with air/O_2 as it is in patients receiving N_2O/O_2 (inspired O_2 concentration [F_{IO_2}] 0.5). They speculated that fentanyl acts on central or peripheral opiate receptors and that this action is not affected by 50% N_2O. In contrast, Pearcy et al. (17) noted that administering N_2O/O_2 (70%:30%) to patients who had previously been given up to 300 mg of meperidine intravenously caused a relatively sudden appearance of slow theta or delta activity. When patients were first anesthetized with N_2O and then given intravenous meperidine, there was a slower onset of the EEG changes. This observation suggests at least an additive effect on the EEG of patients given N_2O with meperidine. In the present study, all patients received N_2O/O_2 (70%:30%) at high flows (7–3 L/min) for at least 25 min before the start of the study. Thus, a steady-state N_2O concentration was established in all patients before any EEG measurements, and any interaction between N_2O and sufentanil would be the same in both the normocarbic and hypocarbic groups.

The action of a single intravenous dose of thiopental should be of short duration. Shideman et al. (19), while determining the ability of the liver to metabolize thiopental, found that patients with normal liver function were able to stand unaided 85–251 s after an intravenous dose of thiopental of 4 mg/kg. Price (20), a number of years ago while discussing a paper by Mark (21) on the kinetics of thiopental, observed that "persons given an induction dose of thiopental and nothing more almost always recover consciousness within a 20-min period." More recently, Fragen and Caldwell (22) gave patients an induction dose of thiopental of 4 mg/kg and then maintained anesthesia with N_2O/O_2 plus a mean additional intravenous

dose of thiopental of 3.5 mg/kg. Surgery lasted an average of 23 min, and the patients responded to command 3.4 min after the N_2O was discontinued.

On the basis of the previous observations, in this study EEG measurements were not made until at least 25 min had elapsed from the time the thiopental was administered. It would be expected that after a dose of 4 mg/kg of thiopental, a patient would be awake and responding to commands by that time and that the patient's EEG would be approaching the awake pattern. In confirmation of this expectation it was noted in group 1 (normocarbia, N_2O/O_2 without narcotic) that the descriptors derived from the processed EEG stabilized by 20–25 min after the injection of thiopental and continued so throughout the entire study period. In view of this observation, we believe thiopental did not influence the experimental results.

A small dose of sufentanil (0.1 μg/kg) was deliberately chosen for this study. We wished, among other things, to determine those EEG descriptors that were most sensitive to narcotic administration. Had a large dose of sufentanil (2–4 μg/kg) been administered as a bolus dose or by infusion there would have been such marked changes in the EEG pattern that all descriptors would significantly change from control, and it would not be possible to determine those descriptors most sensitive to narcotic effect.

A bolus injection technique also permitted precise determination of both time of onset and time to maximum EEG effect of sufentanil. An alternative technique would be the use of an infusion of sufentanil to achieve a steady-state EEG response to the drug and then alter blood pH by changing ventilation. This method would permit us to design a crossover study in which each patient would serve as his or her own control. An important disadvantage of the infusion technique, however, is that to achieve a steady state, one must a priori select a specific EEG descriptor and then adjust the infusion to maintain this descriptor in a steady state. Because we wished to determine which EEG descriptor or descriptors were most sensitive to the narcotic, the a priori selection of a specific descriptor to follow the drug effect might well bias such a determination. We therefore believe that the bolus injection of sufentanil best provided the information we desired concerning the sensitivity of the EEG descriptors to sufentanil, their onset times, time to maximum effect, and any differences among these factors caused by changes in the $Paco_2$.

Because many pharmacologic (drug effect), physiologic (CO_2 tension), and pathologic (hypoxia) factors can alter the EEG, care was exercised to either stabilize or avoid these factors. In studying the pharmacodynamics of sufentanil, the one variable was the EEG response to a single bolus dose of sufentanil.

Predictably, hyperventilation alone produced changes in EEG descriptors derived from PSA. The findings in this group of patients reflect a shift in power into lower frequency bands and a decrease in all the spectral edge frequencies. The interesting finding is that changes in the descriptors derived from the anterior and posterior montages tend to mirror one another (Figure 1).

The intravenous administration of the small dose of sufentanil (0.1 μg/kg) produced significant changes in all descriptors within both the normocarbic and hypocarbic groups (the largest percent of change seen in the various power bands). Thus, descriptors derived from PSA of the EEG can detect alteration in the activity of the brain produced by a relatively small dose of narcotic. Again, changes in descriptors in the anterior and posterior montages for each group mirror one another (Figures 2 and 3).

There were also significant differences in the EEG changes after sufentanil administration between the normocarbic and hypocarbic groups. The hypocarbic patients demonstrated a significant increase of power in the delta power band, also in D/(A + B), and a significant decrease in the spectral edge 50 values. This shift of power into a lower frequency band and a decrease in spectral edge frequency most likely represents an increase in the action of sufentanil on the brain of these patients. The observation by Schwartz et al. (4) that hypocarbia should increase the proportion of sufentanil in its active, nonionized state, may explain the more profound EEG response in our hypocarbic patients. In addition, although hypocarbia unquestionably produces cerebral vasoconstriction, this degree of vasoconstriction does not appear to alter the time to onset of EEG effect or the time to maximum effect for any descriptor.

This study confirms that PSA of the EEG is a sensitive measure of the effects of hypocarbia and a small dose of narcotic on the brain. Further, the data suggest that either the anterior or posterior montage is equally useful in following EEG changes produced by hypocarbia or intravenous injection of sufentanil. In addition, the PSA descriptors—delta power band, spectral edge 50, and relative power in delta power band divided by alpha plus beta power bands—are statistically the most useful after EEG changes induced by sufentanil. Finally, hypocarbia appears to intensify the EEG response to the narcotic sufentanil.

References

1. Nishitateno K, Ngai SH, Finck AD, Berkowitz BA. Pharmacokinetics of morphine: concentrations in the serum and brain of the dog during hyperventilation. Anesthesiology 1979;50: 520–3.

2. Ainslie SG, Eisele JH, Corkill G. Fentanyl concentrations in brain and serum during respiratory acid-base changes in the dog. Anesthesiology 1979;51:293–7.
3. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 1983;62:966–74.
4. Schwartz AE, Matteo RS, Ornstein E, Young WL, Thornhill M. Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. Br J Anaesth 1989;63:385–8.
5. Faulconer A, Pender JW. Influence of partial pressure of nitrous oxide on the depth of anesthesia and the electroencephalogram in man. Anesthesiology 1949;10:601–9.
6. Stockard JJ, Bickford RG. The neurophysiology of anaesthesia. In: Gordon E, ed. A basis and practice of neuroanaesthesia. Amsterdam: Elsevier, 1981:4–49.
7. Yamamura T, Sukuda M, Takeya H, Goto Y, Furukawa K. Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man. Anesth Analg 1981;60:283–8.
8. Fink M. Quantitative pharmaco-EEG to establish dose-time relations in clinical pharmacology. In: Hermann W, ed. Electroencephalography in drug research. Stuttgart: Gustav Fischer, 1982;17–22.
9. Gibbs FA, Williams D, Gibbs EL. Modification of cortical frequency spectrum by changes in CO_2, blood sugar and O_2. J Neurophysiol 1940;3:49–58.
10. Davis H, Wallace WM. Factors affecting changes produced in electroencephalogram by standardized hyperventilation. Arch Neurol Psychiatry 1942;47:606–25.
11. Geddes IC, Gray TC. Hyperventilation for the maintenance of anaesthesia. Lancet 1959;2:4–6.
12. Smith NT, Dec-Silver H, Sanford TJ, et al. EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia. Anesth Analg 1984;63:386–93.
13. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62:234–41.
14. Bovill JG, Sebel PS, Wauquier A, Rog P. Electroencephalographic effects of sufentanil anaesthesia in man. Br J Anaesth 1982;54:45–52.
15. Smith NT, Westover CJ Jr, Quinn M, Benthuysen JL, Dec-Silver H, Sandford TJ Jr. An electroencephalographic comparison of alfentanil with other narcotics and with thiopental. J Clin Monit 1985;1:236–44.
16. Kubickl ST, Freund G, Henschel FW, Schoppenhorst M. Fentanyl und Sufentanil im elektroenzephalographischen Vergleich. Anaesthesist 1977;26:333–42.
17. Pearcy WC, Knott JR, Bjurstrom RO. Studies on nitrous oxide, meperidine and levallorphan with unipolar electroencephalography. Anesthesiology 1957;18:310–5.
18. Sebel PS, Bovill JG, Wauquier A, Rog P. Effects of high-dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 1981;55:203–11.
19. Shideman FE, Kelly AR, Lee LE, Lowell VF, Adams BJ. The role of the liver in the detoxification of thiopental (pentothal) by man. Anesthesiology 1949;10:421–8.
20. Price HL. Discussion of thiobarbiturates. In: Papper EM, Kitz KJ, eds. Uptake and distribution of anesthetic agents. New York: McGraw-Hill, 1963:298.
21. Mark LC. Thiobarbiturates. In: Papper EM, Kitz RJ, ed. Uptake and distribution of anesthetic agents. New York: McGraw-Hill, 1963:289–97.
22. Fragen RJ, Caldwell N. Comparison of a new formulation of etomidate with thiopental: side effects and awakening times. Anesthesiology 1979;50:242–4.

Pipecuronium-Induced Neuromuscular Blockade During Nitrous Oxide-Fentanyl, Enflurane, Isoflurane, and Halothane Anesthesia in Surgical Patients

Mohamed Naguib, MB, BCh, MSc, FFARCSI, MD, Mohamed Seraj, MB, BCh, DA, FFARCSI, and Essam Abdulrazik, MB, BCh, MSc

Department of Critical Care Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, United Arab Emirates, and Department of Anaesthesia, King Khalid University Hospital, Saudi Arabia

This study was designed to determine the capacity of several anesthetics to augment pipecuronium neuromuscular blockade. The potency of pipecuronium was determined with single-bolus administration of 20–50 μg/kg in 160 patients. Patients were anesthetized with N_2O/O_2 (60:40) supplemented with fentanyl (4–5 μg/kg), halothane (0.8%), isoflurane (1.2%), or enflurane (1.7%). Neuromuscular blockade was measured by an acceleration-responsive transducer (the Accelograph, Biometer International, Odense, Denmark). Responses were defined in terms of percent depression in first-twitch height and train-of-four response, and the dose-response curves were constructed after probit transformation of the responses. The dose-response curves were found to be parallel for both first twitch height and train-of-four responses. The dose-response lines for the enflurane and isoflurane groups were displaced significantly ($P < 0.01$) to the left of the line for the fentanyl-N_2O group. The calculated doses producing 50% depression of first twitch height were 21.9, 21.2, 18.9, and 17.8 μg/kg for the N_2O-fentanyl, halothane, isoflurane, and enflurane groups, respectively. Corresponding calculated doses for 50% depression of train-of-four response were significantly smaller (15.5, 14.4, 13.7, 11.9 μg/kg, respectively). The enhancing effects of the volatile anesthetics were reflected by significant prolongation of the clinical duration of neuromuscular blockade by pipecuronium. It is concluded that the potency of pipecuronium is enhanced more by enflurane and isoflurane than halothane or fentanyl-N_2O anesthesia.

(Anesth Analg 1992;75:193–7)

The relative potency of pipecuronium during administration of various anesthetics is not clear. The reported estimated doses producing 95% depression of twitch tension (ED_{95} doses) during nitrous oxide (N_2O)-narcotic anesthesia have ranged from 48.7 μg/kg (1) to 59.4 μg/kg (2). In addition, discrepancies in dose-response results were reported for the effect of isoflurane on the potency of pipecuronium (1,2). Wierda et al. (1) reported that the ED_{95} for pipecuronium was 44.6 μg/kg in patients anesthetized with N_2O/O_2 and 3% isoflurane (inspired concentration). Pittet et al. (2) reported a similar value (42.3 μg/kg) in patients anesthetized with N_2O/O_2 and 0.9% isoflurane. Furthermore, there are no data available for the effects of enflurane or quantitative comparisons of the effects of the four commonly used anesthetics on the neuromuscular block produced by pipecuronium.

This study was designed to determine the dose-response relation of pipecuronium during fentanyl-N_2O/O_2, enflurane-N_2O/O_2, isoflurane-N_2O/O_2, and halothane-N_2O/O_2 anesthesia.

Methods

After institutional approval, 160 ASA physical status group I and II adult patients (80 male, 80 female) were studied. All patients were undergoing elective procedures, had no neuromuscular, renal, or hepatic disease, and were not taking any drug known to interfere with neuromuscular function. Informed consent was obtained. All patients received 2 mg of oral lorazepam 90 min preoperatively. An intravenous infusion of lactated Ringer's solution was established

The results of this study were presented in part at the 10th World Congress of Anaesthesiologists, The Hague, The Netherlands, June 1992.

Accepted for publication March 31, 1992.

Address correspondence to Dr. Naguib, Department of Critical Care Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, P.O. Box 17666, Al Ain, United Arab Emirates.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Demographic Data for 160 Patients Undergoing Elective Surgery

	Enflurane	Isoflurane	Halothane	Fentanyl-N_2O
Age (yr)	32.1 (8.2)	33.3 (7.6)	35.9 (6.5)	33.9 (8.2)
Weight (kg)	65.3 (5.1)	63.6 (5.7)	63.3 (4.5)	62.4 (4.4)
Gender (M/F)	20/20	20/20	20/20	20/20

Age and body weight are presented as means (SD).

before induction of anesthesia. Routine monitoring was used. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C.

Patients were randomly assigned to one of the following anesthetic groups (n = 40 in each): N_2O-fentanyl, N_2O-enflurane, N_2O-isoflurane, or N_2O-halothane. Stratified sampling was used to obtain an even gender distribution. Anesthesia was induced with thiopental (5 mg/kg) and was maintained with N_2O and O_2 (60:40) supplemented with fentanyl (4–5 μg/kg IV), enflurane, isoflurane, or halothane via a face mask. The trachea was sprayed with 4 mL of 4% lidocaine and was intubated without the use of muscle relaxants. After intubation, the end-tidal concentration of the volatile anesthetics was adjusted to 1 MAC (excluding N_2O). The resulting end-tidal concentrations were 1.7% for enflurane, 1.2% for isoflurane, and 0.8% for halothane. The concentrations of the volatile anesthetics, N_2O, O_2, and CO_2 were determined continuously by a multiple-gas analyzer (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal CO_2 pressure [$P_{ET}CO_2$] 35–40 mm Hg).

The acceleration transducer, 5 × 10 mm in size and weighing 20 g, is a piezoelectric ceramic wafer with an electrode on each side (Biometer International, Odense, Denmark) that was fastened to the volar side of the interphalangeal joint of the thumb (3,4). When the wafer experiences acceleration, a voltage difference develops between the two electrodes, and this voltage can be measured and recorded directly. The ulnar nerve was stimulated at the wrist with square-wave supramaximal stimuli of 0.2-ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 15 s. A free movement during evoked thumb adduction was allowed by fixation of the extended four ulnar fingers by an elastic band. On stimulating the ulnar nerve, the transducer was set in motion, and a voltage developed that was proportional to the acceleration. The resulting electrical signal was analyzed by the Accelograph (Biometer International). The TOF values were displayed and recorded. The first twitch (T1) of the TOF was considered the twitch height.

After end-tidal anesthetic concentration was stable for 30 min, we administered at random one of the selected doses of pipecuronium (20, 30, 40, or 50 μg/kg) intravenously as a free-flowing bolus dose. Ten patients were studied at each dose level in each of the four anesthetic groups. The neuromuscular response to pipecuronium was recorded as the maximum depression of T1 and TOF expressed as a percent of the control value. Once the maximum effect of the selected initial dose was reached (that is, when no further decrease in evoked response to three consecutive stimuli occurred), a supplementary dose was chosen so that together with the selected initial dose, a total of 50 μg/kg was administered to all patients. Time to maximum effect (the time from injection of the selected dose to maximum effect) and time from injection of the full dose (50 μg/kg) to 10% recovery of the twitch height (clinical duration) were recorded.

The percent values for T1 and TOF depression were transformed to probits and plotted against the logarithm of the dose of pipecuronium with PCNONLIN (5). Regression lines were compared with analysis of covariance. First, we tested the lines to determine whether they deviated from parallelism; if they did not, an F-test was applied to determine whether the elevations were different. If so, a t-test was applied to determine which line differed in elevation (6) with a BMDP statistical package (1990). The ED_{50} and ED_{95} values (doses causing 50% and 95% depression of twitch tension and TOF ratio, respectively) were calculated from the log-probit regression lines for each anesthetic group. Using analysis of variance, we compared age, body weight, onset time, and clinical duration among anesthetic groups. For all statistical comparisons, differences were considered significant when $P < 0.05$.

Results

Results are expressed as means (SD). There was no significant difference among the four groups with respect to age or weight (Table 1).

Figures 1 and 2 show dose-response curves for the first-twitch height (T1) and TOF response, respectively. For all groups, the regression lines did not deviate from parallelism but differed in position ($P < 0.0001$). The dose-response regression lines of pipecuronium for the enflurane and isoflurane groups

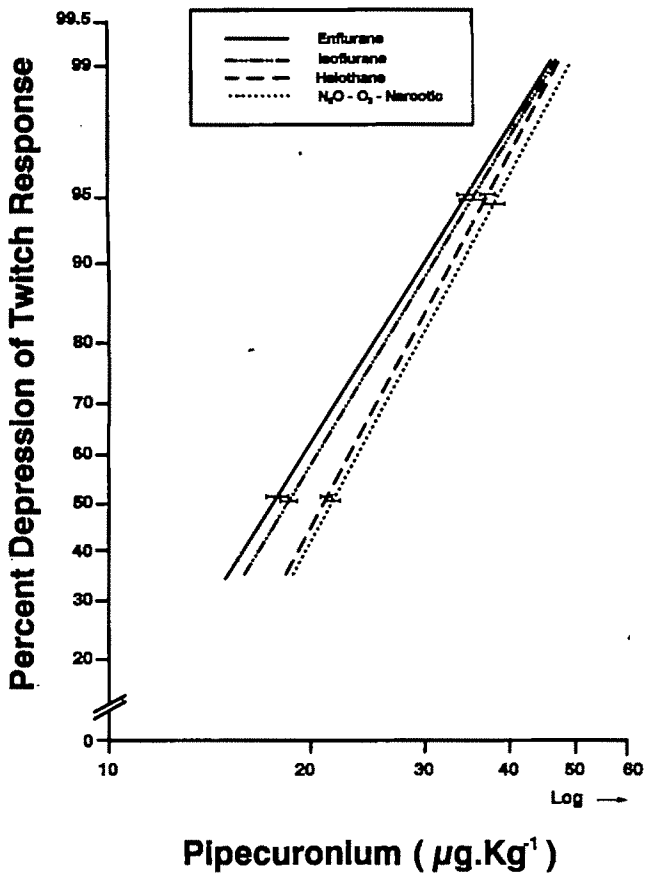


Figure 1. Dose-response relation for twitch height (T1) for pipecuronium during fentanyl-N_2O/O_2, halothane-N_2O/O_2, isoflurane-N_2O/O_2, and enflurane-N_2O/O_2 anesthesia. The *horizontal lines* at the ED_{50} and ED_{95} levels indicate 95% confidence limits.

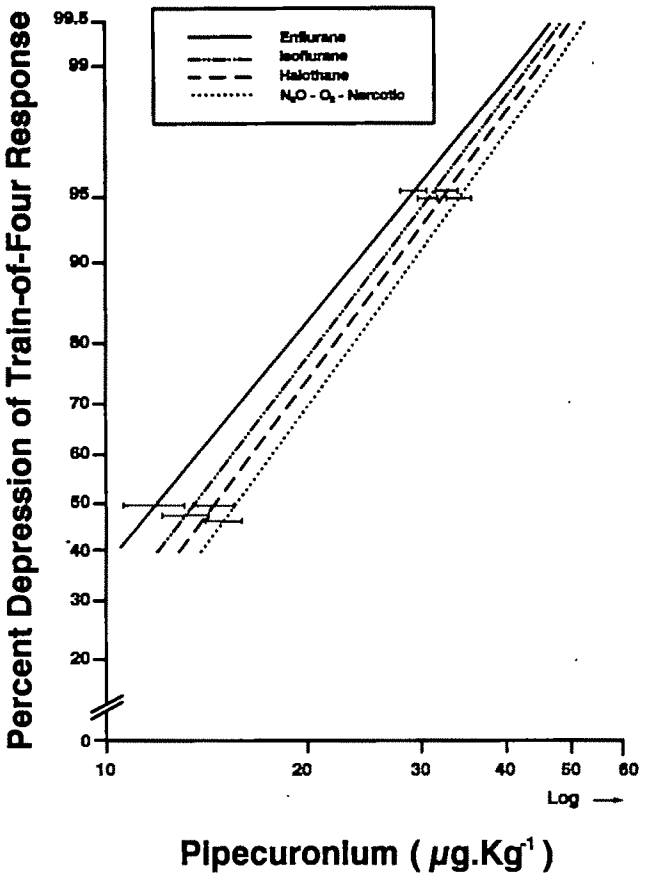


Figure 2. Dose-response relation for train-of-four (TOF) response for pipecuronium during fentanyl-N_2O/O_2, halothane-N_2O/O_2, isoflurane-N_2O/O_2, and enflurane-N_2O/O_2 anesthesia. The *horizontal lines* at the ED_{50} and ED_{95} levels indicate 95% confidence limits.

were shifted significantly ($P < 0.01$) to the left of that for the fentanyl-N_2O/O_2 group. Calculated ED_{50} and ED_{95} values are presented in Table 2. The calculated ED_{50} and ED_{95} values of pipecuronium for TOF response were significantly smaller than those for the T1 response (the 95% confidence limits did not overlap).

The time to maximum effect for pipecuronium in patients receiving N_2O and fentanyl, halothane, isoflurane, and enflurane was 6.3 (0.5), 4.2 (0.7), 3.8 (0.5), and 2.7 (0.4) min, respectively, and was statistically different ($P < 0.01$) among all groups. The clinical duration of the total 50-μg/kg dose for these groups was 29.4 (4.5), 39.5 (4.7), 50.9 (4.5), and 62.9 (4.4) min, respectively, and was statistically different ($P < 0.01$) among the four groups.

Discussion

The results of the present study demonstrate that compared with fentanyl-N_2O/O_2 anesthesia, enflurane and isoflurane but not halothane enhance the neuromuscular blocking effect of pipecuronium. It also demonstrates that the potency of pipecuronium does not differ by >23% from the four anesthetic techniques used in this study. Our findings are consistent with those of Pittet et al. (2) who reported that isoflurane but not halothane enhanced the potency of pipecuronium. In contrast, Wierda et al. (1) found that the estimated ED_{95} doses for pipecuronium during N_2O/O_2 and isoflurane, halothane, or droperidol/fentanyl were not different and were, respectively, 44.6, 46.9, and 48.7 μg/kg. This apparent lack of significant difference among the ED_{95} doses has been attributed to the brevity of exposure of their patients to the anesthetic (10–15 min) before the administration of pipecuronium (1).

The potency of nondepolarizing relaxants depends on the volatile anesthetic used, the method of monitoring neuromuscular function (7), and even geographic location (8). We found that TOF ED_{50} and ED_{95} values were significantly less than that of the T1 response (Table 2). Recent investigations (9) indicated that the calculated ED_{90} and ED_{95} values of ORG 9426

Table 2. Effective Doses of Pipecuronium for 50% (ED_{50}) and 95% (ED_{95}) Depression of Twitch Height (T1) and Train-of-Four (TOF) Response (and Their 95% Confidence Limits) During Enflurane, Isoflurane, Halothane, and Fentanyl-N_2O Anesthesia

	Depression of T1 (% control value)				Depression of TOF response			
	Enflurane	Isoflurane	Halothane	Fentanyl-N_2O	Enflurane	Isoflurane	Halothane	Fentanyl-N_2O
ED_{50} (μg/kg)	17.8 (17.1–18.5)	18.9 (18.3–19.5)	21.2 (20.7–21.7)	21.9 (21.4–22.4)	11.9 (10.7–13.2)	13.7 (12.7–14.8)	14.4 (13.5–15.4)	15.5 (14.7–16.4)
ED_{95} (μg/kg)	35 (33.8–36.3)	35.9 (34.7–37.2)	37.3 (36.1–38.5)	39 (37.8–40.3)	28.7 (27.5–30)	30.8 (29.6–32.1)	31.9 (30.6–33.2)	33.9 (32.5–35.3)

were significantly less with the TOF mode of stimulation compared with the single-twitch stimulation. Ali and Savarese (10) showed that the dose-response curve for *d*-tubocurarine shifted to the left as the frequency of stimulation was increased. This could be attributed to a stimulation-induced increase in the muscle blood flow that would increase delivery of the drug to the neuromuscular junction. Dose-response relations obtained after TOF stimulation may be of more importance than after single-twitch stimulation, because the former is a more sensitive indicator of neuromuscular blockade (11,12).

In this study, the calculated first-twitch ED_{50} doses during fentanyl-N_2O/O_2, halothane, and isoflurane anesthesia were 21.9, 21.2, and 18.9 μg/kg, respectively. Similar values (27.3, 22.7, and 20.6 μg/kg, respectively) were reported by Wierda et al. (1) who used a single-twitch mode of stimulation and mechanomyography and by Pittet et al. (2) (31.7, 25, and 18 μg/kg, respectively) who used electromyography and cumulative technique to construct the dose-response curve.

The range of values reported for the ED_{95} has been greater than for the ED_{50} (1,2). This variability can be attributed to the difficulty of accurately defining the extreme ranges of the dose-response curve and to the differences in the anesthetic techniques and stimulation frequency used by various investigators.

We found that at 1 MAC value, enflurane and isoflurane were similar in enhancing the neuromuscular blockade induced by pipecuronium (Table 2). The first-twitch ED_{50} of pipecuronium was approximately 19% less during enflurane (17.8 μg/kg) and 14% less during isoflurane (18.9 μg/kg) than that during fentanyl-N_2O anesthesia (21.9 μg/kg). This is consistent with the effect of these volatile anesthetics on other nondepolarizing muscle relaxants (11–14) despite the differences in end-tidal concentration of volatile agents used in these various studies.

Several investigators demonstrated that enflurane and isoflurane equally augmented a neuromuscular blockade induced by pancuronium or *d*-tubocurarine and that both anesthetics were approximately twice as potent as halothane (14–16). On the other hand, Rupp et al. (17) found that the volatile anesthetics interact differently with vecuronium than with other nondepolarizing muscle relaxants. At 1.2 and 2.2 MAC levels of anesthesia (which included the MAC contribution from 70% N_2O), enflurane was more potent than either isoflurane or halothane in augmenting a vecuronium-induced neuromuscular blockade, but the effects of isoflurane and halothane were similar (17). Several studies have compared the potency of atracurium during various anesthetic conditions (18–20). Rupp et al. (18) concluded that the potency of atracurium was not different during halothane-N_2O and enflurane-N_2O anesthesia. In contrast, Sokoll et al. (20) found that the ED_{50} of atracurium was 40% less during isoflurane anesthesia than during N_2O-fentanyl anesthesia. Isoflurane (21) and enflurane (22) were shown to have a potentiating effect on the dose-response relation of mivacurium. This is also consistent with the known effect of these volatile anesthetics on *d*-tubocurarine, pancuronium, pipecuronium, and possibly atracurium.

In vitro, halothane and isoflurane potentiate the effects of neuromuscular blocking agents to the same extent (23). In contrast, in vivo, isoflurane produces more potentiation than does halothane (16). This was attributed to an increased muscle blood flow produced by isoflurane. Possible mechanisms by which inhaled anesthetics may exert their effect include depression of the central nervous system, presynaptic inhibition of acetylcholine mobilization and release, postsynaptic receptor desensitization, and an action on the muscle at some point distal to the cholinergic receptor (24,25). Stanec and Baker (26) noted that volatile anesthetics and nondepolarizing muscle relaxants may have synergistic prejunctional actions at the neuromuscular junction.

The time to development of maximal block and the clinical duration of the total dose of 50 μg/kg were dependent on the type of anesthetic used. In this respect, the potentiation of the neuromuscular effects of pipecuronium may be ranked as follows: enflurane > isoflurane > halothane > fentanyl.

We used the Accelograph to monitor the neuromuscular effects of pipecuronium. The Accelograph is based on a new measuring principle: measurement of force is replaced by measurement of acceleration. The principle behind the use of the accelerometer for measuring neuromuscular transmission is Newton's second law: Force = Mass × Acceleration. Because the mass involved is constant, the acceleration is proportional to the force. Therefore, a TOF ratio, for example, measured by means of the acceleration transducer, should in theory correspond to a TOF ratio determined by a measurement of force (4). Viby-Mogensen et al. (3) noted that the relation between force displacement transducer-derived TOF responses and acceleration transducer-derived TOF responses is better than that between force displacement transducer-derived TOF responses and electromyography-derived TOF. Similarly, May and colleagues (27,28) reported that the acceleration transducer is equal to the force displacement transducer with regard to precision and accuracy in clinical recordings.

In conclusion, we have demonstrated that the potency of pipecuronium is enhanced by enflurane and isoflurane but not halothane when compared with fentanyl-N_2O/O_2 anesthesia. The duration of neuromuscular blockade induced by pipecuronium was significantly influenced by the anesthetic technique in the following decreasing order: enflurane > isoflurane > halothane > fentanyl.

We thank Lorraine Ritchie for expert secretarial assistance. Pipecuronium was supplied by Organon Teknika, Belgium.

References

1. Wierda JMKH, Richardson FJ, Agoston S. Dose-response relation and time course of action of pipecuronium bromide in humans anesthetized with nitrous oxide and isoflurane, halothane, or droperidol and fentanyl. Anesth Analg 1989;68: 208–13.
2. Pittet J-F, Tassonyi E, Morel DR, Gemperle G, Richter M, Rouge J-C. Pipecuronium-induced neuromuscular blockade during nitrous oxide-fentanyl, isoflurane, and halothane anesthesia in adults and children. Anesthesiology 1989;71:210–3.
3. Viby-Mogensen J, Hensen E, Werner M, Nielsen K. Measurement of acceleration: a new method of monitoring neuromuscular function. Acta Anaesthesiol Scand 1988;32:45–8.
4. Jensen E, Viby-Mogensen J, Bang U. The Accelograph: a new neuromuscular transmission monitor. Acta Anaesthesiol Scand 1988;32:49–52.
5. Statistical Consultants, Inc. PCNONLIN and NONLIN84: software for the statistical analysis on nonlinear models. American Statistician 1986;40:52.
6. Armitage P. Statistical methods in medical research. 1st ed. London: Blackwell, 1971:269–301.
7. Blackman JG. Stimulus frequency and neuromuscular block. Br J Pharmacol 1963;20:5–16.
8. Fiset P, Donati F, Balendran P, Meistelman C, Lira E, Bevan DR. Vecuronium is more potent in Montreal than in Paris. Can J Anaesth 1991;38:717–21.
9. Cooper RA, Mirakhur RK, Elliott P, McCarthy G. Estimation of the potency of ORG 9426 using two different modes of nerve stimulation. Can J Anaesth 1992;39:139–42.
10. Ali HH, Savarese JJ. Stimulus frequency and dose-response curve to *d*-tubocurarine in man. Anesthesiology 1980;52:36–9.
11. Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular blockade in humans. Br J Anaesth 1970;42: 967–78.
12. Waud BE, Waud DR. The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. Anesthesiology 1972;37:314–22.
13. Gencarelli PJ, Miller RD, Eger EI II, Newfield P. Decreasing enflurane concentrations and *d*-tubocurarine neuromuscular blockade. Anesthesiology 1982;56:192–4.
14. Fogdall RP, Miller RD. Neuromuscular effects of enflurane, alone and combined with *d*-tubocurarine, pancuronium and succinylcholine in man. Anesthesiology 1975;42:173–8.
15. Miller RD, Eger EI II, Way WL, Stevens WC, Dolan WM. Comparative neuromuscular effects of Forane and halothane alone and in combination with *d*-tubocurarine in man. Anesthesiology 1971;35:38–42.
16. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anaesthesia in man. Anesthesiology 1980;35:509–14.
17. Rupp SM, Miller RD, Gencarelli P. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane and halothane anesthesia in humans. Anesthesiology 1984;60:102–5.
18. Rupp SM, McChristian JW, Miller RD. Neuromuscular effects of atracurium during halothane-nitrous oxide and enflurane-nitrous oxide anesthesia in humans. Anesthesiology 1985;63:16–9.
19. Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981;53:45–54.
20. Sokoll MD, Gergis SD, Mehta M, Ali NM, Lineberry C. Safety and efficacy of atracurium (BW33A) in surgical patients receiving balanced or isoflurane anesthesia. Anesthesiology 1983;58:450–5.
21. Weber S, Brandom BW, Powers DM, et al. Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 1988;67:495–9.
22. Caldwell JE, Kitts JB, Heier T, Fahey MR, Lynam DP, Miller RD. The dose-response relationship of mivacurium chloride in humans during nitrous oxide-fentanyl or nitrous oxide-enflurane anesthesia. Anesthesiology 1989;70:31–5.
23. Vitez TS, Miller RD, Eger EI II, Way WL. An in-vitro comparison of halothane and isoflurane potentiation of neuromuscular blockade. Anesthesiology 1974;41:53–6.
24. Waud BE, Waud DR. The effects of diethyl ether, enflurane, and isoflurane at the neuromuscular junction. Anesthesiology 1975;42:275–80.
25. Waud BE, Waud DR. Comparison of the effects of general anesthetics on the end-plate of skeletal muscle. Anesthesiology 1975;43:540–7.
26. Stanec A, Baker MS. Prejunctional effects of potent inhalation anesthetics in man and cat (abstract). Anesthesiology 1987;67: A336.
27. May O, Nielsen HK, Werner MU. The acceleration transducer—an assessment of the precision in comparison with a force displacement transducer. Acta Anaesthesiol Scand 1988;32: 239–43.
28. Werner MU, Nielsen HK, May O, Hernes M. Assessment of neuromuscular transmission by the evoked acceleration response. An evaluation of the accuracy of the acceleration transducer in comparison with a force displacement transducer. Acta Anaesthesiol Scand 1988;32:395–400.

Halothane and Isoflurane Inhibit Endothelium-Dependent Relaxation Elicited by Acetylcholine

Hiroshi Toda, MD, Kumi Nakamura, MD, Yoshio Hatano, MD, Makoto Nishiwada, MD, Masahiro Kakuyama, MD, and Kenjiro Mori, MD, FCANAES

Department of Anesthesia, Kyoto University Hospital, Sakyo-ku, Kyoto and Department of Anesthesiology, Wakayama Medical College, Wakayama-shi, Japan

The purpose of this study was to determine whether volatile anesthetics modify the release of endothelium-derived relaxing factor. We examined the effects of halothane and isoflurane on endothelium-dependent relaxation and 3',5'-cyclic guanosine monophosphate formation elicited by acetylcholine and ionophore A23187 in isolated rat aorta. Halothane and isoflurane (1%–2%) significantly attenuated acetylcholine-induced relaxation of the phenylephrine-contracted aorta but had no significant effect on relaxation induced by A23187, nitroprusside, and nitroglycerin. Basal and A23187 (10^{-7} M)-stimulated levels of 3',5'-cyclic guanosine monophosphate were slightly lowered by halothane and isoflurane (2%). In contrast, the increase of 3',5'-cyclic guanosine monophosphate elicited by acetylcholine (10^{-5} M) was significantly attenuated by halothane (2%) and abolished by isoflurane (2%). These findings indicate that halothane and isoflurane strongly inhibit the release of endothelium-derived relaxing factor elicited by acetylcholine.

(Anesth Analg 1992;75:198–203)

Vascular endothelium releases endothelium-derived relaxing factor (EDRF) (1), which relaxes vascular smooth muscle by activation of 3',5'-cyclic guanosine monophosphate (cyclic GMP, cGMP) (2,3). Anesthetics, including local anesthetics (4), volatile anesthetics (5–7), and barbiturates (8), affect EDRF formation; however, the effects of volatile anesthetics, particularly isoflurane, on EDRF formation appear to be controversial. Muldoon et al. (5), using rabbit aorta and canine femoral and carotid arteries, demonstrated that halothane inhibited endothelium-dependent relaxation elicited by acetylcholine and bradykinin. Moreover, Stone and Johns (6) demonstrated that the relaxant effects of halothane, isoflurane, and enflurane tended to be increased after denudation of the endothelium, suggesting that these anesthetics may inhibit basal production of EDRF or prostacyclin (PGI_2) or stimulate the formation of endothelium-derived constricting factor. In contrast, Blaise et al. (7), using canine epicardial coronary artery, observed that the inhibitory effect of isoflurane on prostaglandin $F_{2\alpha}$-induced contraction was abolished by endothelial denudation, suggesting that isoflurane induced the release of EDRF or facilitated its action.

Although the level of EDRF can be estimated from the level of cGMP in vascular smooth muscle (2,3), little information is available about the effects of anesthetics on cGMP formation in vascular smooth muscle (9,10). Therefore, we examined the effects of halothane and isoflurane on endothelium-dependent relaxation and the basal or stimulated level of cGMP in rat aortas.

Methods

The protocol was approved by the Kyoto University Animal Use Committee. Male Wistar rats weighing 250–350 g were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg) and killed by exsanguination. A preliminary study suggested that administration of pentobarbital at this dose and exsanguination do not affect endothelial integrity. The chest of each rat was opened, and the descending portion of the thoracic aorta was isolated and cut into helical strips approximately 17 mm long for mechanical testing or cut longitudinally into pairs of strips approximately 30 mm long for determination of cGMP. Each strip was then bathed in a 10-mL organ

This study was presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1991.

Accepted for publication March 11, 1992.

Address correspondence to Dr. Nakamura, Department of Anesthesia, Kyoto University Hospital, Sakyo-ku, Kyoto 606-01, Japan.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

bath containing Krebs' bicarbonate solution with the composition (in mM): NaCl 118.2, KCl 4.6, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 24.8, dextrose 10. The bathing fluid was aerated with a mixture of 95% O_2 and 5% CO_2 to keep the pH within the range 7.35–7.45 and maintained at 37 ± 0.5°C. Before the start of the experiments, each strip was allowed to equilibrate for 60–90 min, during which time the fluid was replaced every 15 min. Halothane and isoflurane were introduced into the O_2-CO_2 mixture through Fluotec 3 (Cyprane Keighley, England) and Fortec (Cyprane Keighley), respectively, and their concentrations were measured and adjusted with an Atom 303 anesthetic agent monitor (Atom Co., Tokyo, Japan). In our previous study (11) using the same method of halothane and isoflurane administration, the concentrations of halothane and isoflurane dissolved in the bathing fluid measured by gas chromatography reached equilibrium within 10 and 15 min, respectively.

For the mechanical experiments, each strip was vertically fixed between two hooks under a resting tension of 1.0*g*, and the hook anchoring the upper end was connected to the lever of a force-displacement transducer (Toyo Baldwin T7-240, Japan); change in isometric tension was displayed on an ink-writing oscillograph (Rectigraph 8K, Nihondenki-Sanei Co., Japan). To confirm the integrity of the endothelium, moderate constriction was induced with phenylephrine (3×10^{-7} M), and when the tension had been stabilized, acetylcholine (10^{-6} M) was added to the bathing fluid, followed by papaverine (10^{-4} M); strips in which acetylcholine-induced relaxation was >60% of that induced by papaverine were considered to have intact endothelium and were used in the study. After washing with fresh bathing fluid every 10 min at least three times, each strip was pretreated with 10^{-5} M indomethacin for 15 min to avoid formation of prostanoids, including PGI_2. Subsequently, contraction was again induced with phenylephrine (3×10^{-7} M), and when the tension had been stabilized, one of the relaxants, acetylcholine (10^{-8} to 10^{-5} M), ionophore A23187 (3×10^{-8} to 10^{-6} M), nitroglycerin (10^{-9} to 10^{-6} M), or sodium nitroprusside (10^{-9} to 10^{-5} M), was added cumulatively to the bathing fluid. In the anesthetic-treated groups, the bathing fluid was aerated continuously with a gas mixture containing halothane or isoflurane for 20 min before and during application of relaxants. At the end of the response to each relaxant, 10^{-4} M papaverine was added to the bathing fluid, and the relaxation induced by each concentration of relaxant was compared as a percentage relative to the maximal relaxation induced by papaverine. A preliminary study had shown that the effects of acetylcholine, nitroglycerin, and nitroprusside were restored completely by washing, whereas that of A23187 persisted even after repeated washing. Therefore, the response to A23187 was measured only once in each strip. The responses to acetylcholine, nitroglycerin, and nitroprusside were examined twice or more in each strip, and the orders of the control, halothane, and isoflurane studies were randomized.

For determination of cGMP, one pair of strips was obtained from each rat; one of each pair was used for treatment with halothane or isoflurane and the other was used as a control. Both were suspended in the organ bath without tension, and after a 60-min equilibration period, the bathing fluid was aerated continuously with gas containing halothane (2%) or isoflurane (2%) 20 min before and during exposure to acetylcholine or A23187. Subsequently (for the basal level), 1 min after administration of acetylcholine (10^{-5} M) or 2 min after administration of A23187 (10^{-7} M), the strips were quick-frozen in liquid nitrogen and homogenized in 6% trichloroacetic acid. After ether extraction and succinylation (12), the samples were radioimmunoassayed for cGMP with a Yamasa cGMP assay kit (Yamasa Shoyu Co., Chiba, Japan).

Drugs used were halothane (Takeda Pharmaceutical Co., Osaka, Japan), isoflurane (Dainabot, Osaka, Japan), acetylcholine (Daiichi Pharmaceutical Co., Tokyo, Japan), A23187 (Sigma, St. Louis, Mo.), nitroglycerin (Green Cross Co., Osaka, Japan), sodium nitroprusside (Nacalai Tesque, Kyoto, Japan), indomethacin (Sigma), and papaverine hydrochloride (Dainippon Pharmaceutical Co., Osaka, Japan). A23187 was dissolved in dimethylsulfoxide, the final concentration of which was <0.01%. Indomethacin was dissolved in ethanol, the final concentration of which was <0.1%. In a preliminary study, 0.1% dimethylsulfoxide or ethanol did not induce any effect on tension. Acetylcholine and sodium nitroprusside were dissolved in distilled water. Tubes and organ baths containing sodium nitroprusside were covered with black paper to prevent light degradation. Drugs except halothane and isoflurane were diluted with distilled water as necessary and added directly to the bathing fluid; the volume added was <100 μL (1% of the bathing fluid).

All results are expressed as mean values ± SEM. The effects of anesthetics on cGMP levels were analyzed statistically by Student's *t*-test for paired data. Other data were analyzed statistically by analysis of variance and the Newman-Keuls multiple-range test. Differences at $P < 0.05$ were considered significant.

Results

Phenylephrine (3×10^{-7} M)-induced precontractions averaged 560 ± 33 mg ($n = 34$) in control strips, 520 ± 101 mg ($n = 7$) and 456 ± 78 mg ($n = 24$) in strips

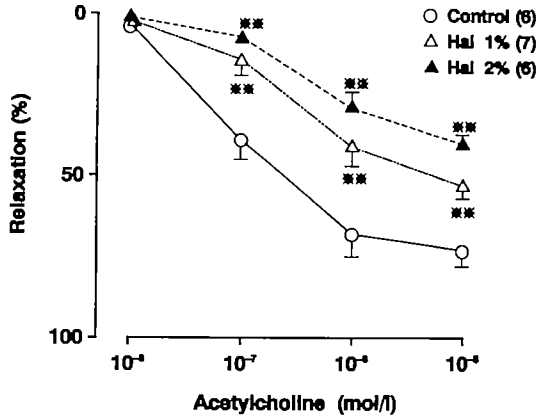


Figure 1. Modification by halothane (Hal) (1% and 2%) of acetylcholine-induced relaxation. Maximal relaxation induced by papaverine (10^{-4} M) was taken to be 100%, the absolute value of which averaged 468 ± 88 mg (n = 6) in control, 543 ± 115 mg (n = 7) in 1% halothane-treated, and 399 ± 87 mg (n = 6) in 2% halothane-treated strips. **P < 0.01 versus control.

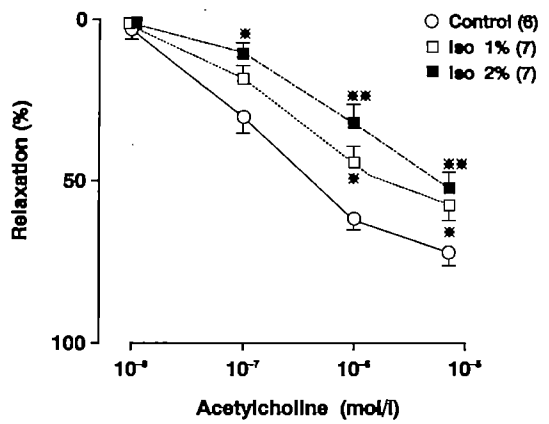


Figure 2. Modification by isoflurane (Iso) (1% and 2%) of acetylcholine-induced relaxation. Maximal relaxation induced by papaverine (10^{-4} M) was taken to be 100%, the absolute value of which averaged 500 ± 57 mg (n = 6) in control, 419 ± 36 mg (n = 7) in 1% isoflurane-treated, and 323 ± 103 mg (n = 7) in 2% isoflurane-treated strips. *P < 0.05, **P < 0.01 versus control.

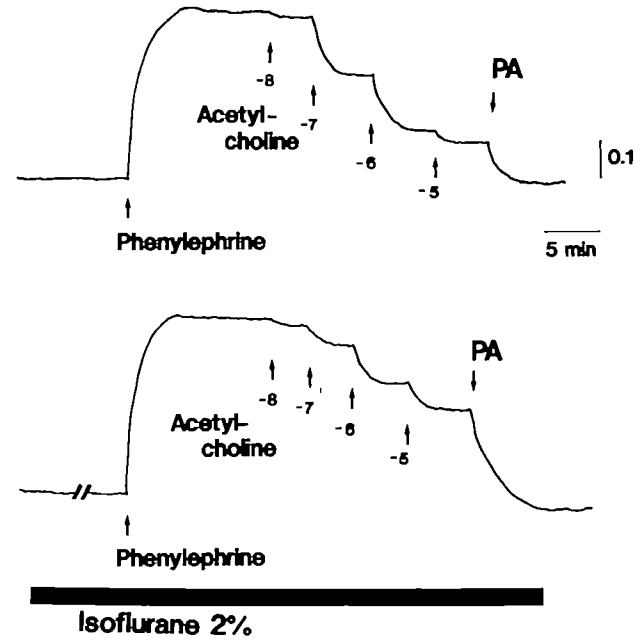


Figure 3. Actual recording of change in tension induced by acetylcholine (10^{-8} to 10^{-5} M) of aortic strip untreated or treated with isoflurane (2%). Numbers indicate concentrations of acetylcholine in log (M). PA, 10^{-4} M papaverine.

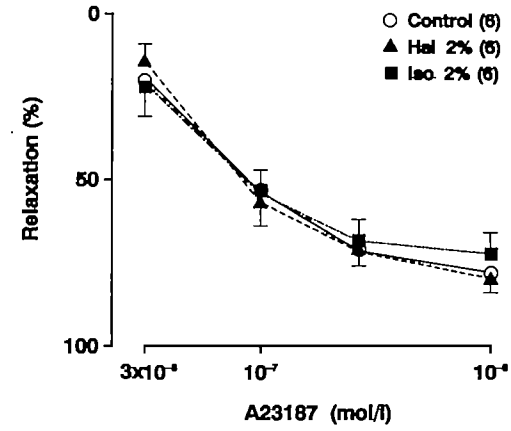


Figure 4. Modification by halothane (Hal) (2%) and isoflurane (Iso) (2%) of A23187-induced relaxation. Maximal relaxation induced by papaverine (10^{-4} M) was taken to be 100%, the absolute value of which averaged 522 ± 69 mg (n = 6) in control, 379 ± 82 mg (n = 6) in 2% halothane-treated, and 468 ± 48 mg (n = 6) in 2% isoflurane-treated strips.

treated with halothane at 1% and 2%, respectively, and 387 ± 54 mg (n = 7) and 441 ± 45 mg (n = 25) in those treated with isoflurane at 1% and 2%, respectively. Acetylcholine (10^{-8} to 10^{-5} M), A23187 (3×10^{-8} to 10^{-6} M), nitroglycerin (10^{-9} to 10^{-6} M), and sodium nitroprusside (10^{-9} to 10^{-5} M) induced concentration-dependent relaxations of phenylephrine (3×10^{-7} M)-precontracted aortic strips. The concentration-relaxant response curve for acetylcholine was shifted upward by halothane and isoflurane (1%–2%) in a concentration-dependent manner (Figures 1 and 2). A typical recording is shown in Figure 3. In contrast, the relaxing response to A23187 relative to that to papaverine (10^{-4} M) was not significantly altered by halothane (2%) or isoflurane (2%) (Figure 4). The responses to nitroglycerin or sodium nitroprusside did not differ between control and halothane (2%)- or isoflurane (2%)-treated strips (Figures 5 and 6).

Table 1 shows the cGMP contents of aortic strips without stimulation and those of strips stimulated by acetylcholine (10^{-5} M) and by A23187 (10^{-7} M). The cGMP levels of strips stimulated by acetylcholine (10^{-5} M) were significantly reduced by exposure to halothane (2%) and isoflurane (2%) (Figure 7). Cyclic GMP levels under basal and A23187 (10^{-7} M)-

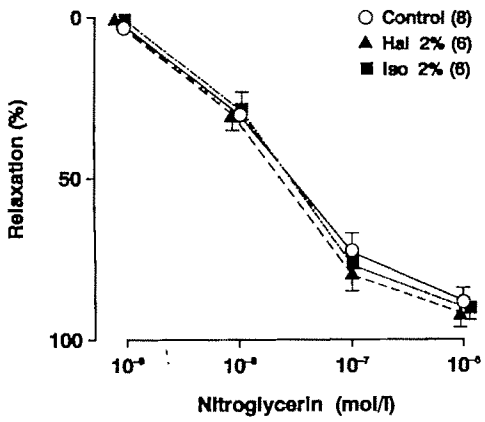


Figure 5. Modification by halothane (Hal) (2%) and isoflurane (Iso) (2%) of relaxation induced by nitroglycerin. Maximal relaxation induced by papaverine (10^{-4} M) was taken to be 100%, the absolute value of which averaged 626 ± 43 mg (n = 8) in control, 430 ± 55 mg (n = 6) in 2% halothane-treated, and 547 ± 89 mg (n = 6) in 2% isoflurane-treated strips.

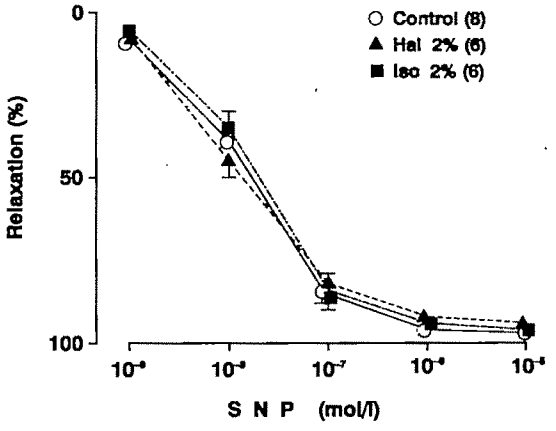


Figure 6. Modification by halothane (Hal) (2%) and isoflurane (Iso) (2%) of relaxation induced by sodium nitroprusside (SNP). Maximal relaxation induced by papaverine (10^{-4} M) was taken to be 100%, the absolute value of which averaged 699 ± 85 mg (n = 8) in control, 455 ± 68 mg (n = 6) in 2% halothane-treated, and 598 ± 17 mg (n = 6) in 2% isoflurane-treated strips.

stimulated conditions were slightly reduced by exposure to halothane (2%) and isoflurane (2%).

Discussion

Vascular endothelium plays an important role in the regulation of vascular tone by releasing relaxants and constrictors, including EDRF (1–3), PGI_2 (13), and endothelin (14). Endothelium-derived relaxing factor is now considered to be identical to nitric oxide (NO) (15,16), which is formed by NO synthase from L-arginine in the endothelium, and activates guanylate cyclase to form cGMP in vascular smooth muscle, which induces relaxation (2,3). Moreover, it has been reported recently that NO is formed not only in the endothelium but also in the central nervous system (17,18), macrophages (19), neutrophils (20), and even vascular smooth muscle (21,22).

Formation of NO is activated by an increase of intracellular free Ca^{2+} in the endothelium elicited on stimulation of specific receptors located on the endothelial cell membrane, application of Ca^{2+} ionophores, and physical stimulation, such as stretching of the endothelium (23). Furthermore, it is known that NO is formed in the endothelium even without stimulation (3), resulting in a higher cGMP level in the aorta with intact endothelium than in endothelium-denuded aorta under basal conditions. In the present study, the basal level of cGMP in rat aorta

Table 1. Cyclic GMP (cGMP) Contents of Rat Aortic Strips With or Without Stimulation, Unexposed or Exposed to Halothane (2%) or Isoflurane (2%)

Stimulus for cGMP formation	Anesthetic	cGMP content (pM/g wet wt)
None (n = 8)	None	64.4 ± 9.1
	Hal (2%)	56.2 ± 6.5
ACh (10^{-5} M) (n = 6)	None	288.7 ± 64.4
	Hal (2%)	117.9 ± 27.2*
A23187 (10^{-7} M) (n = 7)	None	121.7 ± 13.6
	Hal (2%)	99.3 ± 13.2
None (n = 7)	None	70.1 ± 7.4
	Iso (2%)	55.5 ± 10.5
ACh (10^{-5} M) (n = 8)	None	317.8 ± 96.8
	Iso (2%)	49.1 ± 7.5*
A23187 (10^{-7}) (n = 7)	None	116.1 ± 19.0
	Iso (2%)	86.7 ± 12.0

Hal, halothane; Iso, isoflurane; ACh, acetylcholine.
*$P < 0.05$ vs without anesthetic.

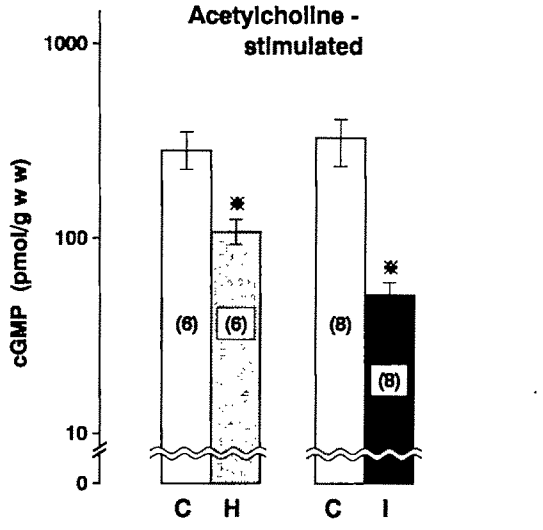


Figure 7. Cyclic GMP (cGMP) contents of rat aortic strips after 1-min exposure to acetylcholine (10^{-5} M). *$P < 0.05$ versus control (C) (n = 6 and 8). H, halothane (n = 6); I, isoflurane (n = 8); gww, grams wet weight.

with intact endothelium was slightly decreased by 2% halothane, although in our previous study (9), halothane increased the cGMP content of rat aorta whose endothelium had been removed. This difference in the effects of halothane on cGMP levels in the presence and absence of endothelium could be explained by the view that halothane increased the endothelium-independent formation of cGMP but decreased the endothelium-dependent basal production of cGMP, resulting in a slight decrease in the total level of cGMP in vascular smooth muscle with intact endothelium.

Blaise and coworkers (7) demonstrated that isoflurane inhibited the contraction induced by prostaglandin $F_{2\alpha}$ in dog epicardial coronary artery with intact endothelium but not in endothelium-denuded artery and hypothesized that isoflurane caused the release of EDRF or facilitated its action on vascular smooth muscle. However, the present study clearly showed that the basal level of cGMP was not increased but was slightly decreased by isoflurane, at least in the absence of vasoconstrictors. This result indicates that in rat aorta, isoflurane does not stimulate EDRF formation, although the involvement of PGI_2 formation cannot be ruled out. This is in good agreement with the findings of Brendel et al. (10) who used rat aorta and may suggest that isoflurane modifies endothelium-dependent relaxation differently in rat aorta and canine coronary artery.

Ionophores increase the permeability to divalent cations of intracellular organelles, such as the sarcoplasmic reticulum, and that of the plasma membrane, resulting in increase of intracellular free Ca^{2+} and other divalent metal cations. The ionophore A23187 at low concentrations induces an increase of cytosolic free Ca^{2+} in endothelial cells but not in vascular smooth muscle, causing endothelium-dependent relaxation of vessels (3). However, at high concentrations, it induces an increase of free Ca^{2+} in vascular smooth muscle cells, causing endothelium-independent constriction (24,25). The increase of intracellular free Ca^{2+} elicited by the ionophore also activates various endothelial enzymes, including phospholipase (26), which may modify the responses to the ionophore.

In our study, the A23187 (10^{-7} M)-stimulated level of cGMP in strips exposed to halothane (2%) and isoflurane (2%) was slightly lower than in unexposed strips, although the relaxation induced by A23187 (3×10^{-8} to 10^{-6} M) was not significantly affected by halothane or isoflurane. In contrast, Uggeri and Johns (27) observed that halothane did attenuate the endothelium-dependent relaxation elicited by A23187 (10^{-8} to 10^{-7} M). The discrepancy between our findings and theirs may be explained partly by the assumption that the potency of the inhibitory effect of anesthetics on EDRF formation differed quantitatively, depending on experimental conditions, or that other nonspecific effects of the ionophore modified the responses differently in the two studies.

Our present work clearly demonstrated that isoflurane and halothane attenuated acetylcholine-induced relaxation and cGMP formation in vascular smooth muscle. Precontractions induced by phenylephrine (3×10^{-7} M) were smaller in strips treated with halothane or isoflurane than in control strips, because these anesthetics have an inhibitory effect on contractions in vascular smooth muscle (6,9,11). However, the attenuation of the response to acetylcholine by anesthetics cannot be ascribed to the diminished precontractions, because relaxing responses to nitroglycerin and sodium nitroprusside relative to the maximal response to papaverine did not differ in control and 2% anesthetic-treated strips. Moreover, as nitro compounds, including nitroglycerin and sodium nitroprusside, activate guanylate cyclase in vascular smooth muscle directly, these findings indicate that these anesthetics do not exert their inhibitory effect on guanylate cyclase in vascular smooth muscle, but rather on NO synthesis in the endothelium.

The MAC of halothane is lower than that of isoflurane; 2% halothane is approximately 2.2 MAC and 2% isoflurane 1.7 MAC (28). Therefore, the finding that 2% isoflurane abolished the increase of cGMP activated by acetylcholine, whereas 2% halothane attenuated it, indicates that isoflurane inhibits the response to acetylcholine more strongly than an equipotent dose of halothane.

Acetylcholine-induced relaxation and cGMP formation showed a higher susceptibility to both halothane and isoflurane than those induced by the ionophore A23187, suggesting that the action of these anesthetics in the endothelium is not limited to direct inhibition of Ca^{2+}-induced activation of NO synthesis. Because acetylcholine is known to bind to specific receptors on the endothelial plasma membrane that increase the release of Ca^{2+} (29) or increase Ca^{2+} influx through the non-L-type Ca^{2+} channel (30), it appears that these anesthetics affect the receptor for acetylcholine or G-protein (31,32) or directly block the influx or release of Ca^{2+} (33), possibly in addition to their less potent, direct inhibitory effect on NO synthesis. Further study will be required to test this hypothesis and elucidate the responsible mechanisms.

References

1. Furchgott R, Zawadzki D. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–6.

2. Rapoport RM, Murad F. Agonist-induced endothelium-dependent relaxation in rat thoracic aorta may be mediated through cGMP. Circ Res 1983;52:352–7.
3. Martin W, Villani GM, Jothianandan D, Furchgott RF. Selective blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation by hemoglobin and by methylene blue in the rabbit aorta. J Pharmacol Exp Ther 1985;232:708–16.
4. Johns RA. Local anesthetics inhibit endothelium-dependent vasodilation. Anesthesiology 1989;70:805–11.
5. Muldoon SM, Hart JL, Bowen KA, Freas W. Attenuation of endothelium-mediated vasodilation by halothane. Anesthesiology 1988;68:31–7.
6. Stone DJ, Johns RA. Endothelium-dependent effects of halothane, enflurane, and isoflurane on isolated rat aortic vascular rings. Anesthesiology 1989;71:126–32.
7. Blaise G, Sill JC, Nugent M, VanDyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
8. Gerkens JF. Barbiturate inhibition of endothelium-dependent dilatation of blood- and Krebs-perfused rat tail arteries. Eur J Pharmacol 1987;134:293–301.
9. Nakamura K, Hatano Y, Toda H, Nishiwada M, Baek WY, Mori K. Halothane-induced relaxation of vascular smooth muscle: a possible contribution of increased cyclic GMP formation. Jpn J Pharmacol 1991;55:165–8.
10. Brendel JK, Proctor G, Johns RA. Isoflurane does not vasodilate rat thoracic aortic rings by EDRF or other cyclic GMP mediated mechanisms (abstract). Anesthesiology 1991;75: A534.
11. Hatano Y, Nakamura K, Yakushiji T, Nishiwada M, Mori K. Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. Anesthesiology 1990;73:513–7.
12. Honma M, Satoh T, Takezawa J, Ui M. An ultrasensitive method for the simultaneous determination of cyclic AMP and cyclic GMP in small-volume samples from blood and tissue. Biochem Med 1977;18:257–73.
13. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxidase to an unstable substance that inhibits platelet aggregation. Nature 1976;263:663–5.
14. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411–5.
15. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524–6.
16. Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacological and chemical properties that are identical to those for nitric oxide radical. Circ Res 1987;61:866–79.
17. Knowles RG, Palacios M, Palmer RMG, Moncada S. Formation of L-arginine in the central nervous system: a transducer mechanism for stimulation of the soluble guanylate cyclase. Proc Natl Acad Sci USA 1989;86:5159–62.
18. Bredt DS, Hwang PM, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 1990;347:768–70.
19. Hibbs JB, Taintor RR, Vavrin Z, Rachlin EM. Nitric oxide: a cytotoxic activated macrophage effector molecule. Biochem Biophys Res Commun 1988;157:87–94.
20. Wright CD, Mulsch A, Busse R, Osswald H. Generation of nitric oxide by human neutrophils. Biochim Biophys Acta 1989;160:813–9.
21. Wood KS, Buga GM, Byrns RE, Ignarro LJ. Vascular smooth muscle-derived relaxing factor (MDRF) and its close similarity to nitric oxide. Biochem Biophys Res Commun 1990;170:80–8.
22. Schini VB, Vanhoutte PM. L-Arginine evokes relaxations of the rat aorta in both the presence and absence of endothelial cells. J Cardiovasc Pharmacol 1991;17:S10–4.
23. Smiesko V, Kozik J, Dolezel S. Role of endothelium in the control of arterial diameter by blood flow. Blood Vessels 1985;22:247–51.
24. Itoh T, Kanmura Y, Kuriyama H. A23187 increases calcium permeability of store sites more than of surface membranes in the rabbit mesenteric artery. J Physiol 1985;359:467–84.
25. Nishiwada M, Nakamura K, Hatano Y, Mori K. The relaxing effects of barbiturates in vascular smooth muscle of rat aorta. J Anesth 1991;5:380–7.
26. Sivarajan M, Hall ER, Wu KK, Rafelson ME, Manner C. Regulation of intracellular arachidonate in normal and stressed endothelial cells. Biochim Biophys Acta 1984;795:271–6.
27. Uggeri MJ, Johns RA. Halothane attenuates both receptor and non receptor mediated EDRF production in rat thoracic aorta (abstract). Anesthesiology 1990;73:A604.
28. Eger EI. MAC. In: Eger EI, ed. Anesthetic uptake and action. Baltimore: Williams & Wilkins, 1974:1–25.
29. Sakai T. Acetylcholine induces Ca-dependent K currents in rabbit endothelial cells. Jpn J Pharmacol 1990;53:235–46.
30. Takeda K, Klepper M. Voltage-dependent and agonist-activated ionic currents in vascular endothelial cells: a review. Blood Vessels 1990;24:169–83.
31. Flavahan NA, Vanhoutte PM. G-proteins and endothelial responses. Blood Vessels 1990;24:218–29.
32. Robinson-White A, Kobayashi Y. Halothane may suppress the action of G-protein, G_p, in endothelial cells (abstract). Anesthesiology 1991;75:A995.
33. Loeb AL, O'Brien DK, Longnecker DE. Endothelial cell calcium mobilization is altered by volatile anesthetics (abstract). Anesthesiology 1991;75:A533.

Effects on Biliary Tract Pressure in Humans of Intravenous Ketorolac Tromethamine Compared With Morphine and Placebo

H. Krimmer, MD, R. E. S. Bullingham, MBBS, FFARCS, J. Lloyd, BSc, MSc, and H. P. Bruch, MD

Department of Surgery, University of Wurzburg, Wurzburg, Germany; Syntex Research, Institute of International Clinical Research-Europe, Maidenhead, Berkshire, England; and Department of Surgery, University of Lübeck, Lübeck, Germany

This study compared the effect of ketorolac tromethamine with that of morphine and placebo on biliary tract pressure. Intraoperatively, 31 anesthetized patients received either ketorolac (30 mg IV, $n = 16$) or morphine (5 mg IV, $n = 15$) after a cholecystectomy or gallstone removal. Intrabiliary tract pressure was measured 5 min after dosing. Postoperatively, 11 patients who had undergone biliary tract surgery received 10 mg of ketorolac or placebo, according to a randomized crossover design on 2 consecutive days. Intraoperatively, the biliary tract pressure did not change significantly from baseline after ketorolac administration. In the morphine group, there was significant increase in pressure over baseline. Postoperatively, there was no significant difference between ketorolac and placebo. We conclude that ketorolac has little or no effect on biliary tract dynamics; therefore, ketorolac may be a logical choice for analgesia in those situations in which spasm of the biliary tract is undesirable.

(Anesth Analg 1992;75:204–7)

Narcotic agonist drugs, such as fentanyl or morphine, can increase intrabiliary pressure in animals (1,2) and humans (3,4), although the effects of mixed agonist-antagonist opioids may be less (1–3). The use of these drugs can be associated with pain mimicking biliary colic or myocardial infarction in the conscious patient (5) or with failure of contrast medium to pass into the duodenum during intraoperative cholangiography in the anesthetized subject (6). In both circumstances, unnecessary interventions may result from the iatrogenic events. The absence of any effect on biliary tract dynamics would thus be an advantage for an analgesic. Moreover, although narcotic agonists are regularly used to treat biliary colic, an analgesic that does not raise intrabiliary pressure would seem more logical for use in this condition. Ketorolac tromethamine (hereafter referred to as ketorolac) is a nonnarcotic analgesic whose principal mode of action is through prostaglandin synthetase inhibition (7). In the parenteral formulation, doses of 10–30 mg have shown an analgesic efficacy comparable to that of 10 mg of morphine or similar equianalgesic doses of other narcotics (8,9). Because prostaglandins can be involved in both contraction and relaxation of smooth muscle, the resultant action of this class of drugs on the biliary tract is not obvious. We therefore determined the effects of ketorolac compared with those of morphine and placebo in two separate studies. The intravenous route was chosen to ensure total bioavailability of the drugs, although ketorolac is administered largely through the intramuscular route. A dose of 30 mg of ketorolac was used intraoperatively and 10 mg postoperatively because these are the doses most commonly used at these times.

Methods

Male and female subjects undergoing biliary tract surgery were entered into the study. Patients were excluded who had clinically significant cardiovascular or renal disease or who had irreversible liver dysfunction such as cirrhosis. Jaundice per se was not an exclusion criterion. Two studies were conducted concurrently, and patients were entered into one or the

Accepted for publication April 10, 1992.

Address correspondence to Ms. J. Lloyd, Institute of International Clinical Research-Europe, Grenfell House, 13-35 Grenfell Road, Maidenhead, Berkshire SL6 1ER, England.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

other, or both, depending on the type of gallbladder surgery or whether a T-tube drain was inserted and, if so, whether it was maintained until the postoperative study. The study protocols were approved by the hospital ethical committee, and informed consent was obtained from each subject before study entry.

In the intraoperative study, patients were studied immediately after a cholecystectomy or removal of stones from the gallbladder while still anesthetized. The study was of parallel-group, double-blind, randomized design. The two treatment groups received either ketorolac (30 mg IV) (Syntex Research, Maidenhead, U.K.) or morphine (5 mg IV). After intravenous induction, anesthesia was maintained by administration of muscle relaxant and an inhaled anesthetic (halothane, $n = 30$; isoflurane, $n = 1$; enflurane, $n = 4$) with nitrous oxide/oxygen ventilation. To ensure satisfactory anesthetic status, three patients required fentanyl intraoperatively (two in the ketorolac group and one in the morphine group). Biliary tract pressure was measured with a modified Caroli apparatus (3). After two consistent baseline measurements, the intravenous test medication was administered slowly, and the intrabiliary tract pressure measurement repeated 5 min after dosing.

In the postoperative study, patients with biliary tract surgery requiring insertion of a T-tube drain were studied. The study was a two-period crossover double-blind design, with randomized assignment of treatment to periods, and was conducted on days 4 and 5 after surgery. The treatments used in the periods were ketorolac (10 mg IV) and intravenous placebo (ketorolac vehicle containing ethanol, sodium chloride, sodium hydroxide, and water). On the trial days, no narcotic analgesia was allowed in the 4-h period before administration of the test medication. A Statham element pressure transducer was inserted through a catheter into the T-tube, and biliary tract pressure was measured continuously. To ensure a stable baseline, the biliary tract pressure was required to change by <5 mm Hg for a period of at least 10 min before the test medication was administered. After administration, the biliary tract pressure was recorded continuously for 1 h on a chart recorder. The maximal pressure during this time was then noted, and the maximal change in biliary tract pressure was calculated as the maximal minus the baseline value. The time taken for biliary tract pressure to return to control levels was then recorded.

For analysis of the intraoperative study, the mean of the two pretreatment measurements of biliary pressure was used as the baseline value. Statistical comparison between treatment groups of the change from baseline to the 5-min posttreatment biliary pressures was performed using a two-sample t-test. For each treatment group, a within-treatment comparison was also made between the posttreatment and baseline values using a paired t-test. For the crossover design of the postoperative study, the maximal change in biliary pressure from baseline was analyzed with analysis of variance. The model included sequence, patient within sequence, and period effects as well as treatment effects. All statistical tests were two-tailed, with a 5% level of significance.

Table 1. Patient Demography for Intraoperative Study

	Ketorolac (30 mg) ($n = 16$)	Morphine (5 mg) ($n = 15$)
Gender		
Male	4 (25%)	3 (20%)
Female	12 (75%)	12 (80%)
Age (yr)		
Mean	54	56
SEM	3.9	3.4
Range	20–75	31–75
Weight (kg)		
Mean	69	70
SEM	2.8	2.8
Range	47–91	54–86.5

Table 2. Patient Demography for Postoperative Study

Total (n)	11
Ketorolac 10 mg/placebo (n)	5
Placebo/ketorolac 10 mg (n)	6
Gender	
Male	4 (36%)
Female	7 (64%)
Age (yr)	
Mean	60
SEM	2.6
Range	39–74
Weight (kg)	
Mean	72
SEM	4.7
Range	47–99

Four patients entered both studies.

Results

Thirty-five patients entered the intraoperative study, of whom four were excluded from analysis (one patient with liver metastases and three patients with technical problems during the pressure measurements). Of the remaining 31 patients, 16 received ketorolac and 15 received morphine. All patients underwent cholecystectomy. As shown in Tables 1 and 2, the groups were similar for clinical characteristics. Four of these patients were subsequently entered into the postoperative part of the study.

A total of 11 patients entered the postoperative study. Five received ketorolac and six received pla-

Table 3. Intraoperative Biliary Tract Pressures (mm Hg)

	Ketorolac (n = 16)	Morphine (n = 15)
Baseline		
Mean	9.49	9.39
SEM	0.76	0.81
Range	4.88 to 16.47	3.52 to 13.73
Posttreatment		
Mean	8.76	10.98
SEM	0.65	1.10
Range	5.40 to 14.06	3.66 to 18.87
Change (posttreatment − baseline)		
Mean	−0.73	1.59
SEM	0.40	0.40
Range	−5.00 to 1.41	−0.15 to 5.14
P value	0.09	0.001

Comparison between treatments: treatment difference (morphine-ketorolac), 2.32; statistical significance, $P < 0.001$; 95% confidence interval, 1.17 to 3.47.

Table 4. Maximal Increase in Biliary Tract Pressure (mm Hg) in Postoperative Patients

Sequence	Period 1	Period 2	Ketorolac	Placebo
Ketorolac/placebo (n = 5)				
Mean	1.10	0.52	1.10	0.52
SEM	0.71	0.28		
Range	−0.2 to 3.7	−0.1 to 1.4		
Placebo/ketorolac (n = 6)				
Mean	0.25	0.80	0.80	0.25
SEM	0.37	0.28		
Range	−1.2 to 1.1	0.2 to 1.3		
Overall mean[a]			0.95	0.39

Treatment difference (ketorolac-placebo), 0.57; statistical significance, P = 0.26; 95% confidence interval, −0.49 to 1.62; maximum increase = maximum − baseline.

[a]Means adjusted for imbalance in number of patients in each sequence.

cebo in the first period. Ten patients underwent cholecystectomy (including the four studied intraoperatively) and biliary tract surgery; one had common bile duct surgery only. Clinical characteristics are shown in Table 2 and are broadly similar to the intraoperative group.

The results of the intraoperative pressure measurements are shown in Table 3. In the ketorolac treatment group, the small mean decrease in biliary tract pressure did not reach statistical significance. In contrast, the morphine treatment group showed a mean increase in biliary tract pressure that was statistically significant. The between-group comparison showed a statistically significant increase of >2 mm Hg biliary tract pressure with morphine relative to ketorolac.

Table 4 shows the results of the postoperative biliary tract pressure measurements. The pooled mean increase in maximal pressure of 0.57 mm Hg for ketorolac relative to placebo was not statistically significant. The period effect was not significant, and the treatment effect was consistent across periods. On both days, the measured absolute biliary pressures were considered, with one exception, not to have returned to normal levels, and therefore the time taken for this to occur was not recorded.

Discussion

In studying the effect of ketorolac on biliary tract pressure, two separate models were used. Both models have particular advantages and limitations. In the intraoperative study, the measurements were done against a background of immediately preceding surgical interference and multiple other anesthetics. These influences may have moved the baseline away from the resting state so that responsiveness to opioid actions may have been altered. An opioid comparator therefore seems appropriate in this model. It was essential to minimize interference with normal operative procedure, in particular the duration of anesthesia. Therefore, the time between drug administration and pressure measurement had to be kept minimal. A parallel group design and use of the intravenous route were thus prerequisites. The intraoperative use of positive pressure ventilation allows safe intravenous use of the opioid. Because of the time restrictions, measured biliary pressure differences may not be maximal or may not have occurred at the time of maximal pharmacodynamic effect of the study drugs. This is a limitation of the model, and the possibility exists that the maximal effect of ketorolac may have occurred later. A further potential limitation is that only one dose of ketorolac was studied. Previous studies of the pharmacologic effect of different doses of ketorolac have indicated no dose response (10), and therefore only one dose was selected.

In the intraoperative study, the patients underwent a simple cholecystectomy in which the biliary system was not potentially altered by the effects of obstruction and inflammation before surgery. In this model, 5 mg of morphine led to a significant within-patient mean increase in biliary pressure of 1.6 mm Hg, representing a 17% increase from baseline. This is comparable to the 23% increase over baseline with fentanyl (100 μg IV) reported by McCammon et al. (3) who used a similar model and methodology. In contrast, ketorolac (30 mg IV) did not significantly alter biliary pressure. Butorphanol, fentanyl, and nalbuphine all increase biliary pressure (3), although the increase shown with nalbuphine

was not statistically significant. In this model, ketorolac had little or no effect on biliary tract pressure under circumstances in which morphine and other opioids have shown significant increases.

The second model studied patients 4–5 days postoperatively when concomitant medication use is minimal and consists mainly of relatively low doses of analgesics. However, the presence of a T-tube may itself alter biliary tract dynamics; for example, mechanical irritation may alter both smooth muscle responsiveness and bile duct compliance. A crossover design thus seems most appropriate because the occurrence of these factors in a given patient, although unknown, is likely to be consistent over the 24 h or so of the study period and there are also fewer available patients than for the intraoperative model. Carryover effects are unlikely from single doses of ketorolac, whose plasma half-life is 4–6 h (11). The model has the advantage that measurements may be recorded continuously over 1 h or more, allowing definition of both a stable baseline and the maximal effect after drug administration.

Intravenous placebo was used in the postoperative study partly because an active control had been used in the intraoperative study and partly because use of intravenous narcotics in the late postoperative phase is unusual and probably unwarranted. The intravenous ketorolac dose of 10 mg was lower than that used intraoperatively; ketorolac has a flat dose-response curve for analgesia at doses beyond 10 mg, so that the peak effect of 10- and 30-mg doses are not dissimilar (7). Assuming that the same would be true of the effect on the biliary tract, and because maximal effect could be measured, the 10-mg dose was chosen because this is the recommended dose for use in the late postoperative course through both parenteral and oral routes. Compared with placebo, ketorolac showed a small increase in the maximal biliary pressure, although this was not statistically significant. The mean increase seen with ketorolac relative to placebo was 25% of the increase seen with morphine relative to ketorolac, assuming that the responsiveness of the two models was comparable. A poststudy power calculation showed that a difference of 1.31 mm Hg between ketorolac and placebo could be detected. The 95% confidence interval shows that the difference is unlikely to be >1.6 mm Hg.

We conclude that ketorolac has little or no effect on biliary tract dynamics relative to morphine. The analgesic efficacy of ketorolac appears to be as good as that from the usual doses of morphine or other opioid agonists (7). In some clinical situations, spasm of the biliary tract is critically undesirable, such as in retrograde endoscopic biliary procedures. For other situations, an increase in biliary tract pressure seems best avoided, such as in the treatment of postoperative pain after biliary surgery. Ketorolac would then seem a logical choice of analgesic.

References

1. Romo-Solas F, Aldrete JA, Franatovic Y. Effects of butorphanol, fentanyl and morphine on the intrabiliary pressure of guinea pigs. Surg Gynecol Obstet 1980;150:551–4.
2. Roebel LE, Cavanagh RL, Buyniski JP. Comparative gastrointestinal and biliary tract effects of morphine and butorphanol. J Med 1979;10:225–38.
3. McCammon RL, Stoelting RK, Madura JA. Effects of butorphanol, nalbuphine, and fentanyl on intrabiliary tract dynamics. Anesth Analg 1984;63:139–42.
4. Economou G, Ward-McQuaid JN. A cross-over comparison of the effect of morphine, pethidine, pentazocine and phenazocine on biliary pressure. Gut 1971;12:218–21.
5. Land DW, Pilon RN. Naloxone reversal of morphine-induced biliary colic. Anesth Analg 1980;59:619–20.
6. Jones RM, Fiddian-Green R, Knight PR. Narcotic-induced choledochoduodenal sphincter spasm reversed by glucagon. Anesth Analg 1980;59:946–7.
7. Buckley M-T, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1990;39:86–109.
8. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556–61.
9. Folsand B, Skulberg A, Halvorsen P, Helgesen KG. Placebo-controlled comparison of single intramuscular doses of ketorolac tromethamine and pethidine for post-operative analgesia. Int Med Res 1990;18:305–14.
10. Brandon Bravo LJC, Mattie H, Spierdijk J, Bovill JG, Burm AGL. The effects on ventilation of ketorolac in comparison with morphine. Eur J Clin Pharmacol 1988;35:491–4.
11. Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol 1988;35:423–5.

AMBULATORY ANESTHESIA
Section Editor
Patricia A. Kapur

Effects of Ketorolac and Bupivacaine on Recovery After Outpatient Arthroscopy

Ian Smith, FFARCS, Robert A. Shively, MD, and Paul F. White, PhD, MD, FFARACS

Departments of Anesthesiology and Surgery, Washington University School of Medicine, St. Louis, Missouri; and Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas

The effects of intraarticular bupivacaine, systemic ketorolac, and a combination of both treatments on postoperative pain and mobilization were evaluated in 60 healthy outpatients undergoing arthroscopic knee surgery under general anesthesia. After induction of anesthesia, patients received 2 mL of either ketorolac (60 mg) or saline solution (1 mL IV and 1 mL IM). On completion of surgery, the patient's knee joint was injected with 30 mL of either 0.5% bupivacaine or saline solution, according to a randomized, double-blind protocol. Only one patient (6%) receiving both medications complained of pain on awakening, compared with seven patients receiving either bupivacaine (37%) or ketorolac (41%) alone. Postoperative fentanyl was required by significantly fewer patients receiving combined therapy (n = 4, 21%) than either bupivacaine (n = 13, 62%) or ketorolac (n = 12, 60%) alone; however, there were no significant differences among the three treatment groups in terms of perioperative pain, nausea, or sedation visual analogue scale scores. Similarly, there were no differences in the times to ambulation or discharge or in analgesic requirements at home. In conclusion, a combination of systemic ketorolac and intraarticular bupivacaine decreased analgesic requirements and pain on awakening after arthroscopic surgery. However, the use of ketorolac alone or in combination with bupivacaine offered no advantage over bupivacaine alone with respect to recovery times after outpatient arthroscopy.

(Anesth Analg 1992;75:208–12)

The use of intraarticular local anesthetics has been shown to facilitate mobilization and decrease postoperative analgesic requirements after outpatient arthroscopic knee surgery (1). However, the use of local anesthetics does not appear to alter patients' perception of their postoperative pain (1–4). Possible explanations for this finding include pain from sites other than the knee joint (e.g., hip and back pain from patient positioning); loss of local anesthetic solution from the arthroscopy portals; and a peripheral inflammatory response to the surgical stimulus. Thus, it is possible that the use of an analgesic medication with a different site of action may provide improved pain relief after this ambulatory surgical procedure.

Ketorolac tromethamine is a nonsteroidal antiinflammatory drug that has been shown to exert considerable opioid-sparing properties when used to provide analgesia after a wide variety of surgical procedures (5–7). We designed this randomized, double-blind study to investigate the effects of systemic ketorolac, intraarticular bupivacaine, and a combination of both on pain, analgesic requirements, and recovery after outpatient arthroscopic knee surgery.

Methods

Written, informed consent was obtained from 60 healthy outpatients scheduled to undergo arthroscopic knee surgery under general anesthesia. Patients were assigned to one of three treatment groups with a computer-generated random number sequence: group I received systemic saline solution and intraarticular 0.5% bupivacaine (30 mL); group II received systemic ketorolac (60 mg) and intraarticular saline solution; group III received systemic ketorolac (60 mg) and intraarticular 0.5% bupivacaine (30 mL). This randomized, double-blind protocol was approved by the Human Studies Committee at Washington University School of Medicine. Patients with a history of hypersensitivity to local anesthetic or nonsteroidal antiinflammatory agents, as well as those at increased risk for gastrointestinal hemorrhage, were

This work was supported in part by funds from the Ambulatory Anesthesia Research Foundation, Los Altos, California.

Accepted for publication March 31, 1992.

Address correspondence to Dr. White, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9068.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

excluded from participation in the study. All patients fasted for at least 6 h before surgery and received no preanesthetic medication. Before induction of anesthesia, patients completed baseline 100-mm visual analogue scales (VAS) for pain, sedation, and nausea (from 0 = none to 100 = maximal effect).

After insertion of an intravenous cannula and placement of routine intraoperative monitoring devices, patients received a standardized general anesthetic technique, consisting of fentanyl (1 μg/kg) and propofol (2 mg/kg IV) for induction of anesthesia, followed by a variable-rate propofol infusion (50–160 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and nitrous oxide, 67% in oxygen, for maintenance of anesthesia. Patients breathed spontaneously throughout the operation. After induction of anesthesia, patients were given 2 mL of the study medication containing either ketorolac (60 mg) or saline solution (1 mL IV and 1 mL into the deltoid muscle). At the end of the operation, the patient's knee joint was injected through one of the arthroscopy portals with 30 mL of a second solution containing either saline solution or 0.5% bupivacaine. Both study medications were supplied by the hospital pharmacy in numbered syringes, with the anesthesiologist, surgeon, and patient unaware of their contents.

On completion of the operation, the propofol infusion and nitrous oxide were simultaneously discontinued. The times from the end of anesthesia until awakening (defined as spontaneous eye opening), sitting up in a chair, tolerating oral fluids, ambulating, being judged "fit for discharge," and hospital discharge were recorded by an observer unaware of the study technique. Mobilization was facilitated by the use of crutches (all patients received instruction in their use preoperatively). Patients were encouraged to sit up and begin the mobilization process when they felt able, without any predefined time constraints. Patients were considered to be fit for discharge from the postanesthesia care unit (PACU) when they were orientated to time and place, had stable vital signs on sitting up, could void urine, and were able to ambulate (with the use of crutches).

A standard three-lead electrocardiogram was used to monitor heart rate and rhythm during the first 30 min in the PACU. Postoperative pain was treated with fentanyl (25 μg IV) bolus doses. The patients' postoperative requirements for analgesic and antiemetic medications were recorded. Patients were asked "are you in pain?" on arrival in the PACU and at subsequent 15-min intervals, and a simple yes/no answer was recorded. The patients' assessment of postoperative sedation, pain, and nausea was further evaluated with the 100-mm VAS at 15-min intervals after surgery for the first hour of recovery and at the time of discharge. The patients were contacted the day after surgery by a research nurse (also unaware of the study technique) who inquired about their overall physical condition and their use of analgesic medication after discharge from the outpatient surgery center. Finally, patients completed a questionnaire concerning pain, mobilization, and analgesic use at home that was returned (in a preaddressed envelope) on resuming normal activities.

Data are expressed as mean values ± SD. Continuous variables were analyzed with analysis of variance, with Bonferroni's correction applied to multiple comparisons among groups, and descriptive variables were analyzed with the χ^2-test. A P value of <0.05 was considered statistically significant.

Results

There were no significant differences among the three treatment groups with respect to age, weight, height, gender distribution, ASA physical status, duration and nature of surgery, or total dose of propofol administered (Table 1). Preoperative VAS scores for pain, sedation, and nausea were also similar in all three groups. Significantly fewer patients in group III (n = 1, 6%) complained of pain when directly questioned on arrival in the PACU compared with patients in groups I (n = 7, 37%) and II (n = 7, 41%) (P = 0.04) (Figure 1). There was also a significant difference in the number of patients in pain after 30 min in the PACU (Figure 1). In contrast, there was no difference among the groups in their assessment of postoperative pain according to the VAS (Figure 2).

Significantly fewer patients in group III (bupivacaine and ketorolac) required opioid analgesia in the PACU than patients in the other two treatment groups (P = 0.01) (Table 2). These patients also requested medication significantly later than patients in the other two groups (Table 2). More than 75% of all the patients we studied had pain that necessitated the use of oral analgesics at home. There was a tendency for postdischarge analgesic requirements to be higher in patients in group I, although this trend did not reach statistical significance. Three patients (one in group II and two in group III) could not be contacted by telephone the following day.

All three groups of patients had similar times to awakening from anesthesia and did not differ significantly from one another in the times for subsequent recovery events (Figure 3). Patients were judged to be "home ready" at 127 ± 24, 140 ± 29, and 146 ± 35 min from the end of anesthesia in groups I, II, and III, respectively. Follow-up questionnaires were returned by 27 patients (approximately 50% in each group). The analgesic requirements and mobilization patterns of these patients did not differ among the three treatment groups. The median time required for

Table 1. Patient Demographic Characteristics in the Three Treatment Groups

	Group I (Bupivacaine, n = 21)	Group II (Ketorolac, n = 20)	Group III (Bupivacaine + ketorolac, n = 19)
Age (yr)	33 ± 13	34 ± 12	42 ± 12
Weight (kg)	84 ± 22	83 ± 19	77 ± 17
Height (cm)	170 ± 9.3	173 ± 10.5	170 ± 12.3
Gender (M/F)	12/9	14/6	11/8
ASA physical status (I/II)	15/6	19/1	13/6
Baseline analogue scores (mm)			
Pain	11 ± 8	16 ± 10	7 ± 6
Sedation	21 ± 14	14 ± 9	24 ± 14
Nausea	5 ± 4	5 ± 5	5 ± 5
Duration of surgery (min)	33 ± 11	34 ± 15	38 ± 15
Duration of anesthesia (min)	50 ± 12	49 ± 16	54 ± 15
Type of arthroscopic procedure (n):			
Diagnostic	5	3	4
Meniscectomy	7	10	11
Debridement	9	7	4
Total propofol (mg)	577 ± 153	571 ± 195	536 ± 206

M, male; F, female.
Mean values ± SD.

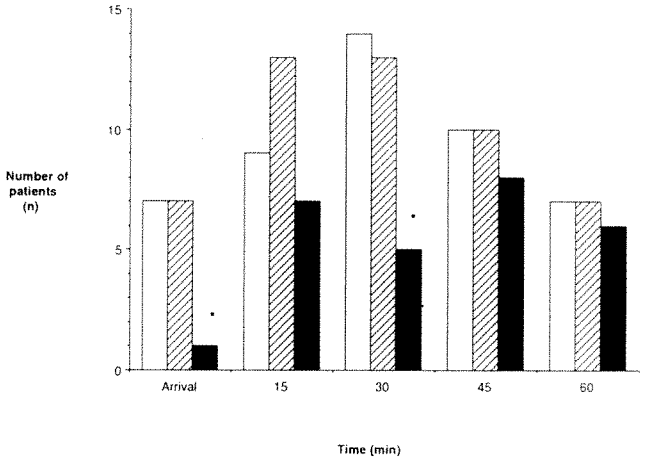


Figure 1. Number of patients reporting pain on arrival in the postanesthesia care unit (Arrival) and at subsequent 15-min intervals. *Open bars*, group I (bupivacaine 0.5%); *hatched bars*, group II (ketorolac); *solid bars*, group III (ketorolac and bupivacaine). *P < 0.05, from groups I and II.

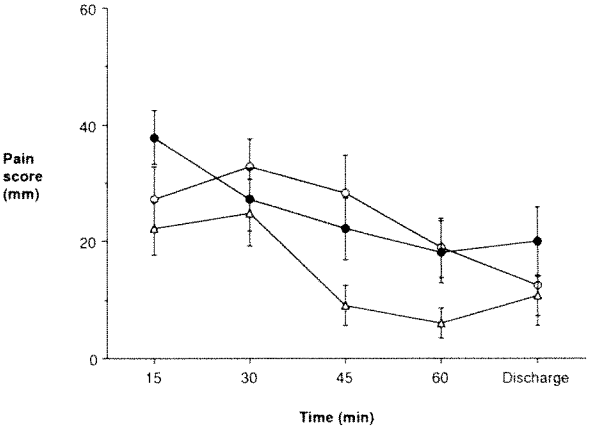


Figure 2. Changes in VAS pain scores from baseline (mean paired differences) at 15, 30, 45, and 60 min after arriving in the PACU, as well as the time of discharge for the three treatment groups. *Open circles*, group I (bupivacaine 0.5%); *solid circles*, group II (ketorolac); *open triangles*, group III (ketorolac and bupivacaine). Mean values ± SEM.

crutch-assisted mobilization was 2 days in each group.

No differences among the three groups were detected in either postoperative nausea or sedation VAS scores. Nausea was uncommon in this patient population, with only three patients requiring antiemetic medication (two in group I and one in group III). No clinical signs or symptoms of local anesthetic toxicity (e.g., cardiac dysrhythmias) were noted in any patient during the early postoperative period. Patient satisfaction was high, with only one patient from each of groups I and II expressing a preference for a different form of anesthesia in the future.

Discussion

Intraarticular bupivacaine (0.5%) and systemic ketorolac (60 mg) appeared to have very similar effects on postoperative pain, mobilization, and analgesic requirements after outpatient arthroscopy. In contrast, the combination of both treatment modalities resulted in fewer patients awakening from anesthesia in pain and significantly decreased requirements for opioid analgesia in the PACU. Despite the improved pain relief in the early postoperative period in group III (vs groups I and II), we were unable to demonstrate a difference in recovery events, postop-

Table 2. Postoperative Analgesic Requirements of Patients in Three Treatment Groups

	Group I	Group II	Group III
Required fentanyl in PACU	13 (62%)	12 (60%)	4 (21%)[a]
PACU fentanyl dose (μg)	83 ± 37	88 ± 31	56 ± 31
First analgesic (min)	34 ± 17	32 ± 15	55 ± 28[a]
Oral analgesic at home	13 (76%)	20 (95%)	13 (68%)

PACU, postanesthetic care unit.
Mean values ± SD.
[a]Significantly different from groups I and II; $P < 0.05$.

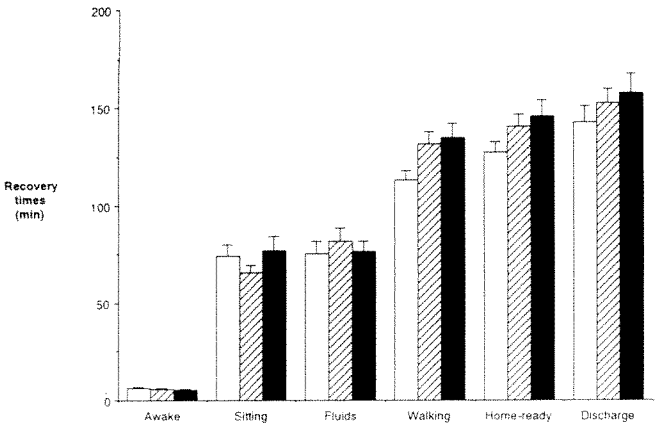


Figure 3. Times from discontinuation of anesthesia until the patients were awake (Awake), able to sit up in a chair (Sitting), tolerate oral fluids (Fluids), ambulate (Walking), "fit for discharge" (Home-ready), and actual discharge (Discharge) were recorded. *Open bars*, group I (bupivacaine 0.5%); *hatched bars*, group II (ketorolac); *solid bars*, group III (ketorolac and bupivacaine). Mean values ± SEM.

erative side effects, or discharge times. Although the decreased opioid requirement in the ketorolac-bupivacaine group might have been expected to decrease emetic sequelae, no difference was found. This finding was probably related to the fact that the incidence of nausea was very low in all three treatment groups.

The lower incidence of pain on awakening from anesthesia in patients receiving the bupivacaine-ketorolac combination (group III) would appear to be a worthwhile advantage. Although pain on emergence from anesthesia can be effectively treated with potent rapid-acting opioid analgesics, other concerns (e.g., transporting the patient to the PACU, connecting patient monitors, and obtaining vital signs) may delay obtaining opioid medication from locked cabinets and lead to inadequate analgesic treatment. Although only minor differences in patients' pain were detected later in the recovery process, the comparable pain scores in groups I and II (vs group III) were achieved by administering larger doses of fentanyl in the PACU. In addition, these patients would have experienced at least brief episodes of more severe pain before the analgesic medication was administered.

In an effort to improve our ability to assess pain, two different methods were used in this study. Immediately on arrival in the PACU, patients may not have been sufficiently recovered from the effects of the propofol anesthetic to reliably assess their pain with the VAS. However, all patients were able to state whether or not they were in acute pain. For consistency, we continued to use this evaluation tool at subsequent assessment intervals to supplement the VAS scores. The differences in these two assessment modalities at the 30-min time point are probably related to greater interpatient variability in the VAS scores compared with simple yes/no responses.

The use of a local anesthetic in combination with a nonsteroidal antiinflammatory drug (ketorolac) provided postoperative pain relief with drugs possessing distinctly different mechanisms of action. The local anesthetic should minimize pain resulting from irritation of nerve endings on the surface of the joint itself. Although ketorolac is alleged to have an effect at this peripheral site, it may also prove to be effective at more remote locations. After knee arthroscopy, most of the pain would be expected to result from the operative joint surface; however, other sources of pain (e.g., the skin puncture wounds, extracapsular structures that were stretched during manipulation, hip and back pain from lying on the operating table) also contribute to postoperative patient discomfort. Furthermore, by administering the ketorolac at the start of surgery, its effects would be expected to peak close to the end of anesthesia (42 ± 14 min after administration of 2 mL of the study drug). The maximal effects of the local anesthetic might not be apparent immediately on emergence from anesthesia because bupivacaine requires several minutes to achieve its peak effect (8). However, instilling the local anesthetic solution into the knee joint before the end of surgery would not have been practical because the drug would have been immediately washed out by the irrigating solution. Given the duration of action of ketorolac and bupivacaine, it was not surprising that no significant analgesic effects were apparent after the patients returned home.

This study can be criticized in that a placebo control was not used. However, in a previous study we demonstrated a decrease in postoperative analgesic requirements and more rapid mobilization when intraarticular bupivacaine (vs saline solution) was used (1). Because this technique has become our standard of care, we decided to use intraarticular bupivacaine as the "control." Although it would appear that each of the three treatments used in this study was equally effective in allowing early mobilization, consideration should be given to the cost of

these postoperative analgesic therapies. The hospital acquisition costs of 30 mL of 0.5% bupivacaine is $1.52, compared with $5.93 for 60 mg of ketorolac. Thus, it would appear that the local anesthetic is more cost-effective than the nonsteroidal antiinflammatory drug.

In conclusion, a combination of systemic ketorolac and intraarticular bupivacaine resulted in fewer patients awakening in pain and a decreased requirement for opioid analgesic medication in the PACU compared with either treatment alone. Although there were no differences among the three analgesic treatments in terms of recovery events and discharge times, the combination of these two analgesic modalities would appear to offer improved patient comfort during the first 30 min after outpatient knee arthroscopy.

We thank our research nurse, Katherine Martin, RN, for help in the postoperative evaluation of the study patients. We also express our sincere thanks to all of the staff in the outpatient pharmacy for their assistance in the preparation of the study medications, especially Nancy Koehler.

References

1. Smith I, Van Hemelrijck J, White PF, Shively R. Effects of local anesthesia on recovery after outpatient arthroscopy. Anesth Analg 1991;73:536–9.
2. Hughes DG. Intra-articular bupivacaine for pain relief in arthroscopic surgery. Anaesthesia 1985;40:821.
3. Milligan KA, Mowbray MJ, Mulrooney L, Standen PJ. Intra-articular bupivacaine for pain relief after arthroscopic surgery of the knee joint in daycase patients. Anaesthesia 1988;43:563–4.
4. Henderson RC, Campion ER, DeMasi RA, Taft TN. Post-arthroscopy analgesia with bupivacaine. Am J Sports Med 1990;18:614–7.
5. Gillies GWA, Kenny GNC, Bullingham RES, McArdle CS. The morphine-sparing effect of ketorolac tromethamine. Anaesthesia 1987;42:727–31.
6. Kenny GNC, McArdle CS, Aitken HH. Parenteral ketorolac: opiate-sparing effect and lack of cardiorespiratory depression in the perioperative patient. Pharmacotherapy 1990;10:127s–31s.
7. Parker RK, Holtmann B, White PF. Effect of ketorolac on the postoperative opioid requirement and recovery profile (abstract). Anesthesiology 1991;75:A758.
8. Meinig RP, Holtgrewe JL, Wiedel JD, Christie DB, Kestin KJ. Plasma bupivacaine levels following single dose intraarticular instillation for arthroscopy. Am J Sports Med 1988;16:295–300.

Echocardiographic Analysis of Dysfunctional and Normal Myocardial Segments Before and Immediately After Coronary Artery Bypass Graft Surgery

Paolo Voci, MD, Federico Bilotta, MD, Solomon Aronson, MD, Giovanni Scibilia, MD, Quintilio Caretta, MD, Corrado Mercanti, MD, Benedetto Marino, MD, Ronald Thisted, PhD, Michael F. Roizen, MD, and Attilio Reale, MD

Sections of Cardiology and Cardiac Surgery, University of Rome "La Sapienza," Rome, Italy, and Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois

Echocardiography has revealed evidence of "subnormal" regional contraction patterns that result from myocardial ischemia and are often accompanied by nonadjacent "hyperkinetic" regions. Whether these regions of hyperkinetic wall motion persist unchanged or revert to normal after coronary artery bypass graft (CABG) surgery has not been studied in humans. Using echocardiography, we evaluated both dysfunctional and normal myocardial regions for changes in segmental wall motion and percent of systolic wall thickening that occurred immediately after CABG surgery in 32 patients. Segmental wall motion analysis before CABG surgery in these patients revealed that 170 (66%) of 256 myocardial segments were subnormal, of which 115 (67%) improved and 102 (60%) returned to normal immediately after CABG surgery. Eleven myocardial segments that were hyperkinetic before CABG surgery returned to normal after CABG surgery. Preoperatively, 162 (63%) of 256 myocardial segments had systolic wall thickening <30%, which increased from 11.8% ± 8.9% to 24.3% ± 14.3% (mean ± SD) ($P < 0.01$) postoperatively. Conversely, a reverse trend was found when systolic wall thickening was >30% before CABG surgery: thickening decreased from 46.2% ± 13.8% to 33.4% ± 14.8% after CABG surgery ($P < 0.01$). Thus, we conclude that immediately after CABG surgery, there is a recovery of function in some myocardial segments and a reduction in function in others. Furthermore, we conclude that the semiquantitative assessment of percent of systolic wall thickening is a more reliable (consistent) echocardiographic index of myocardial function compared with the qualitative assessment of segmental wall motion immediately after CABG surgery.

(Anesth Analg 1992;75:213–8)

The immediate and long-term influence of coronary artery bypass graft (CABG) surgery on a dysfunctional myocardium has been evaluated with two-dimensional echocardiography (1–5). Changes in dysfunctional myocardial systolic wall thickening and segmental wall motion (SWM) have been demonstrated with an immediate, sustained improvement after CABG surgery (2). The functional changes that occur in normal or compensatory hyperkinetic myocardial segments before CABG surgery have not been previously described in humans.

Although the sensitivity of SWM abnormalities for detecting myocardial ischemia has been established, the specificity has been questioned (6–9). The difference between hypokinesis or hyperkinesis and normal function may appear confusing and subjective when SWM is used as an echocardiographic index of ischemia. Semiquantitative methods for evaluating myocardial contraction patterns have been proposed; however, there still remains an element of subjectivity in the interpretation of these methods (10–14). Ideally, one would want to initiate therapy based on an objective index of regional myocardial function. Although an ideal index of ischemia requires measurement of regional myocardial oxygen supply and demand, at the present time only functional parameters such as patterns of segmental myocardial contraction are typically used for echocardiographic assessment of ischemia.

We evaluated the effect of CABG surgery on normal and dysfunctional myocardial regions immediately before and after coronary bypass grafting. In

This work was presented in part at the American Society of Echocardiography Annual Meeting, June 1991, Arlington, Virginia.
Accepted for publication April 10, 1992.
Address correspondence to Dr. Aronson, Department of Anesthesia and Critical Care, University of Chicago, 5841 South Maryland Avenue, Box 428, Chicago, IL 60637.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

addition, we evaluated whether systolic wall thickening (a semiquantitative measurement) provided more reliable information with regard to function of the myocardium after CABG surgery than did changes in SWM (a qualitative measurement).

Methods

Thirty-two patients (29 men, 3 women), whose ages ranged between 38 and 74 yr (mean 59 yr), with documented coronary artery disease were monitored with either epicardial and transesophageal echocardiography or transesophageal echocardiography alone during CABG surgery. The patients were characterized as follows: 14 had one or two diseased vessels; 16 had three or more diseased vessels; and two had left main coronary artery disease. An old transmural myocardial infarction was documented in 15 of the patients (eight inferior, five anteroseptal, and two inferolateral).

Patients with a history or evidence of esophageal disease, including diverticular disease or acute left ventricular dysfunction that required inotropic or vasodilator support before surgery, were excluded from the study. Patients who were dependent on inotropic or vasodilator support after separation from cardiopulmonary bypass (CPB) were also excluded.

Induction of anesthesia was performed with fentanyl (10–15 μg/kg), diazepam (0.25–0.5 mg/kg), oxygen, and succinylcholine (1.5 mg/kg). Maintenance of general anesthesia was accomplished with fentanyl titrated up to a total dose of 70–100 μg/kg before sternotomy. Muscle relaxation was maintained with pancuronium bromide. Systemic arterial blood pressure and heart rate were monitored continuously with an arterial line and electrocardiogram, respectively. Pulmonary capillary wedge pressures were measured with a pulmonary artery catheter. Hematocrit values were obtained before and after separation from CPB at approximately the time of echocardiographic measurements. The surgical technique was not significantly modified at any time during the procedure except when epicardial echocardiographic images were being recorded. The CABG surgery was carried out with systemic hypothermia (25–28°C) during CPB. Distal saphenous vein anastomosis was completed first, after aortic occlusion and anterograde administration of cold potassium crystalloid cardioplegia solution. Additional cardioplegia solution was instilled every 20–30 min throughout the ischemic period through the aortic root as well as through the proximal free end of the grafts immediately after distal anastomosis was completed. Proximal anastomosis was performed during partial aortic occlusion and the rewarming phase of CPB.

Intraoperative echocardiographic images of the left ventricle, short-axis view, at the level of the papillary muscle were obtained and recorded with a General Electric RT-5000 ultrasound system (Milwaukee, Wis.) connected to an epicardial or transesophageal ultrasound transducer (5 MHz) immediately after pericardiotomy and 30 ± 5 min after separation from CPB and administration of protamine. Fifteen minutes were allowed to pass after the administration of protamine before echocardiographic images were recorded. Patients had synchronized atrial and ventricular rhythms at the time of echocardiographic imaging. In addition, administration of inotropes (including calcium) or vasodilators after CPB was avoided or suspended for a minimum of 5 min before recording echocardiographic images.

Epicardial imaging was performed in the initial 14 patients with either a 3.5- or 5.0-MHz gas-sterilized probe. The probe was inserted into a plastic glove partially filled with saline solution to separate the transducer lens from the surface of the heart, thus enabling imaging of the entire left ventricle including the epicardial borders. After the first 14 patients were studied, it was decided that there was no significant gain in performing both epicardial and transesophageal imaging; therefore, the former was discontinued. All 32 patients were monitored with transesophageal echocardiography beginning immediately after intubation throughout the duration of surgery.

Off-line analysis of SWM was performed, and percent of systolic wall thickening determined. The short-axis view of the left ventricle at the level of the papillary muscle was divided into eight segments according to the recommendations of the American Society of Echocardiography (15). Two independent observers unaware of the experimental conditions reviewed the SWMs before and after CABG surgery off-line for each of the eight equally divided segments of all patients. The segments were assessed subjectively and scored on a 0–4-point scale according to the following criteria: 0 = dyskinesia (paradoxical wall motion); 1 = akinesia (absence of wall motion); 2 = hypokinesia (contraction less than normal); 3 = normal; and 4 = hyperkinesia (contraction greater than normal). The system used for SWM analysis was a modification of previously reported floating reference systems (16). A segment was subjectively judged to contract normally if its "imaginary" radius to the center of the left ventricle shortened by at least 30%. A segment was hypokinetic if its radius to the center of the left ventricle shortened by <30% and hyperkinetic if it shortened by >40%. Akinesis was defined as no shortening, and dyskinesis was defined by a radius lengthened to the center of the left ventricle. Analysis for SWM was based on visual estimates of endocardial motion. If there was a disagreement between the two observers on the score of an SWM,

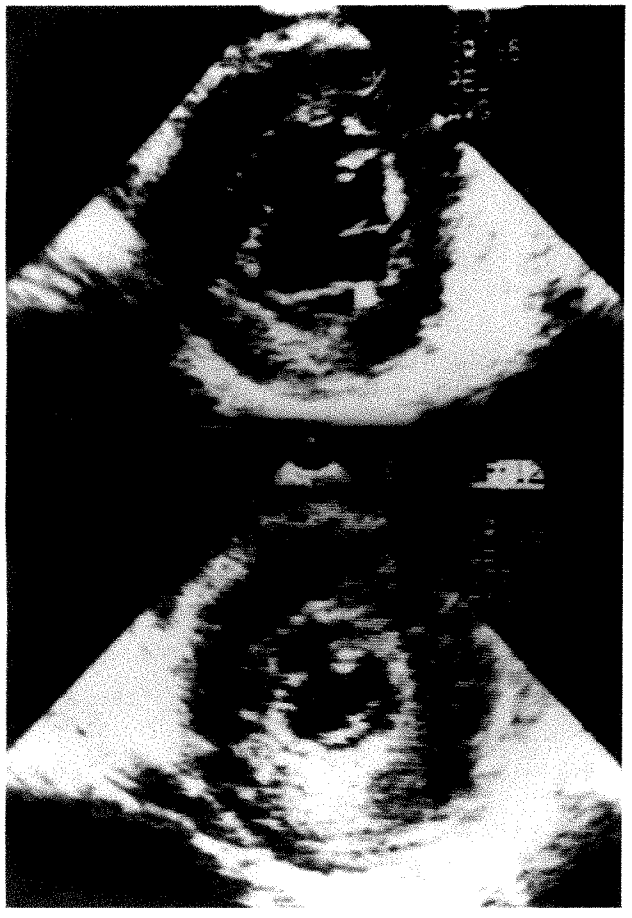


Figure 1. Intraoperative left ventricular short-axis images at mid-papillary muscle level. *Top*, end-diastole; *bottom*, end-systole.

a third independent observer also unaware of the results and conditions of the study reviewed the echocardiogram. The final score assigned for the wall motion of each segment was based on the majority score of the three observers.

Measurement of the percent of systolic wall thickening was made by three independent observers unaware of the experimental conditions. Again, the short-axis view of the left ventricle at the midpapillary muscle level was divided into eight segments. The wall thickness (in the middle of the segment, along the radius drawn through the midsection) was measured within each segment during end-diastole and end-systole. The anterior and posterior papillary muscles and the right ventricle provided a fixed external frame of reference for determination of the midsection of the left ventricular cavity (17). End-diastole was measured when the electrocardiographic-gated freeze-frame analysis of echocardiographic images corresponded to the peak of the electrocardiographic R-wave, and end-systole was measured at the point of minimal left ventricular cavity area (Figure 1). End-diastolic and end-systolic endocardial and epicardial borders were outlined off-line from the video screen with a trackball. The papillary muscles were excluded when the endocardial border was traced. Three measurements for each segment and each observer were averaged. Percent of left ventricular wall thickness was calculated before and after CABG surgery with the following formula:

$$\text{Percentage SWT} = \frac{\text{SWT} - \text{DWT}}{\text{SWT}} \times 100,$$

where SWT and DWT represent systolic and diastolic wall thickness, respectively. Student's *t*-test was used for statistical analysis, and $P \leq 0.05$ was considered significant. All data are expressed as mean ± SD.

Table 1. Hemodynamic Variables Measured at the Time of Echocardiographic Analysis

	Before CABG	After CABG
SBP (mm Hg)	112 ± 7.9	108 ± 12.1
PCWP (mm Hg)	6.4 ± 4.8	8.8 ± 3.2
LVEDA (cm^2)	10.9 ± 0.7	9.7 ± 0.9
HR (beats/min)	62 ± 11	74 ± 13
Hct (%)	38 ± 5	29 ± 9

Before CABG, time before pericardiotomy; After CABG, time after separation from cardiopulmonary bypass; SBP, systolic blood pressure; PCWP, pulmonary capillary wedge pressure; LVEDA, left ventricular end-diastolic area; HR, heart rate; Hct, hematocrit; CABG, coronary artery bypass graft.

Results

The mean CPB time was 127 min (range 46–230) and the mean total ischemic time was 90 min (range 0–160). Epicardial echocardiography lengthened total surgery time by no more than 5 min. Among the 32 patients evaluated, 30 were separated from CPB without requiring supplemental inotropic or vasodilator support; 2 required temporary inotropic support, which was discontinued >5 min before echocardiographic analysis. Hemodynamic variables measured at the time of echocardiographic analysis are shown in Table 1. Systolic arterial blood pressure, a surrogate of afterload, was 112 ± 7.9 mm Hg before and 108 ± 12.1 mm Hg after CABG surgery; pulmonary capillary wedge pressure was 6.4 ± 4.8 mm Hg before and 8.8 ± 3.2 mm Hg after CABG surgery; left ventricular end-diastolic area was 10.9 ± 0.7 cm^2 before and 9.7 ± 0.9 cm^2 after CABG surgery; and heart rate was 62 ± 11 beats/min before and 74 ± 13 beats/min after CABG surgery. The average hematocrit values were 38% ± 5% before CABG surgery (15 min after pericardiotomy) and 29% ± 9% after CABG surgery (30 min after separation from CPB).

With the methods of analysis described for determining the percent of systolic wall thickening, the

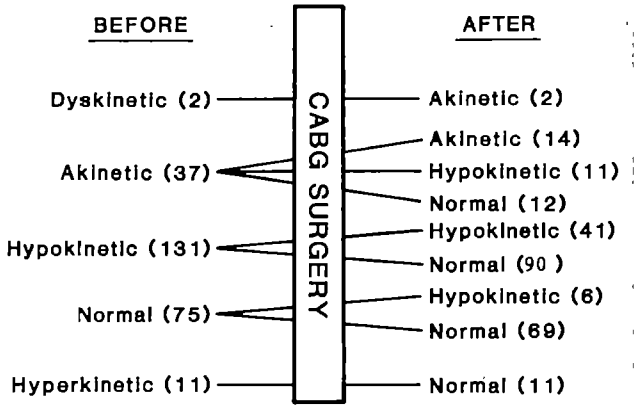


Figure 2. Total number of wall motion scores assigned to myocardial segments before and after CABG surgery.

interobserver variability was 4.6% ± 1.8%, and the intraobserver variability was 1.7% ± 0.7%. Interobserver variability during the evaluation of SWM was evident 9% of the time (45 of 512) and required a third observer to score the wall motion of the segment in question.

The SWM analysis revealed that in the 32 patients, 170 of 256 myocardial segments were subnormal (with scores <3), of which 115 (67%) improved and 102 (60%) returned to normal immediately after CABG surgery. Of the 32 patients, 11 had one hyperkinetic segment (score = 4), that became normal immediately after CABG surgery. No initially abnormal segments before CABG surgery became worse after CABG surgery, and of the 75 initially normal segments (score = 3), six (8%) became hypokinetic after CABG surgery (Figure 2). In one patient there were no subnormal and one hyperkinetic segment. After CABG surgery, the hyperkinetic segment became normal, and two of seven previously normal segments became hypokinetic. The number of abnormal segments in any one patient before CABG surgery was not predictive of changes in SWM after CABG surgery. Intraobserver discordance during SWM analysis occurred in distinguishing normal from hypokinetic (40 of 45), hypokinetic from dyskinetic (4 of 45), and normal from hyperkinetic (1 of 45) segments.

Analysis of systolic wall thickening revealed that in 162 (63%) of 256 segments with systolic wall thickening of <30% before CABG surgery, wall thickening increased from 11.8% ± 8.9% to 24.3% ± 14.3% ($P < 0.01$) after CABG surgery (Figure 3). In the remaining 37% (94 segments) with wall thickening >30%, before CABG surgery, a reverse trend was observed. Percent of systolic wall thickening decreased from 46.2% ± 13.8% to 33.4% ± 14.8% ($P < 0.01$) (Figure 4). There was no significant change

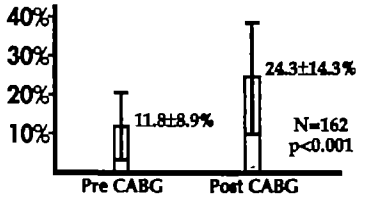


Figure 3. Preoperative (Pre CABG) and postoperative (Post CABG) percent of systolic wall thickening in segments with preoperative systolic wall thickening <30%. Systolic wall thickening increases after surgery in ischemic segments.

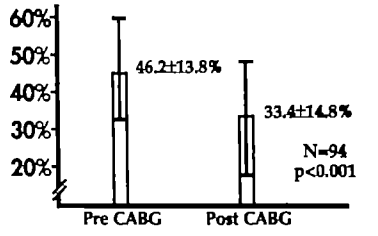


Figure 4. Preoperative (Pre CABG) and postoperative (Post CABG) percent of systolic wall thickening in segments with preoperative systolic wall thickening >30%. Systolic wall thickening decreases after surgery in nonischemic segments.

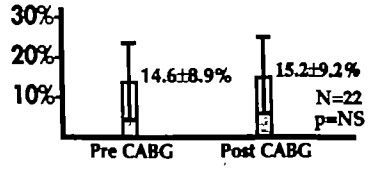


Figure 5. Preoperative (Pre CABG) and postoperative (Post CABG) percent of systolic wall thickening in the segments with previous (old) myocardial infarction. Percent of systolic wall thickening remains unchanged in segments with previous myocardial infarction; NS, not significant.

observed in the percent of wall thickening after CABG surgery in regions of previously infarcted segments ($n = 22$) before CABG surgery (Figure 5).

Discussion

It is well recognized that an early consequence of a decrease in coronary blood flow to the myocardium is the depression of regional function (18–22). After the restoration of adequate blood supply and in the absence of anatomic damage, myocardial function recovers. When ischemia has been prolonged, however, full restoration of blood flow and adequate oxygen supply may occur minutes to hours before the return of normal wall motion to the affected myocardial segment. Evidence from echocardiographic analysis during percutaneous transluminal coronary angioplasty reveals that although SWM abnormalities increase in the regions distal to the vessel undergoing coronary angioplasty, there is hyperkinesis in the

opposing myocardial regions (23). Five minutes after successful coronary angioplasty, observed wall motion abnormalities returned to normal in the reperfused regions. With regard to changes in hypercontracting segments distal to hypocontractile segments, in patients suffering acute myocardial infarction (24) and in patients with ischemic heart disease during lumbar epidural anesthesia (25), hypercontracting segments returned to normal at the same time that the hypocontracting segments improved. Our findings are in accordance with previous reports showing that the surgical restoration of adequate blood supply to an ischemic, hypocontractile myocardium is followed by an immediate improvement in systolic thickening in those regions as well as a return to normal function in a previously nonischemic, hypercontractile myocardium (24,25).

The evaluation of SWM as an index of myocardial function is subjective (2,7,8,15). It is recognized that subtle differences in wall motion are often missed visually (11,12). Differences in SWM abnormalities may be influenced by an unmasked scar caused by changes in afterload (8), a tethering effect caused by neighboring infarcted segments (26), or septal motion (5,27). Measurement of the percent of systolic wall thickening, on the other hand, is less dependent on left ventricular translational and rotational changes and appears to be a more objective parameter for evaluation of left ventricular motion.

Limitations of this study were lack of temporal randomization (i.e., before vs after CABG surgery) for wall motion scoring and a controlled depth of anesthesia before and after CPB. It is reasonable, however, to assume that this latter limitation may have biased the data against our observed results. Endogenous catecholamines would have most likely been highest after separation from CPB, thus causing otherwise normally functioning myocardial segments to behave hyperdynamically. We observed that "hyperkinetic" regions before CABG surgery became less dynamic or normalized after CABG surgery.

Our results suggest that poorly perfused, hypocontracting myocardial segments, as evidenced by the percent of systolic wall thickening, are often counterbalanced before CABG surgery by the hyperkinesis of normally perfused segments. Immediately after CABG surgery, the percent of systolic wall thickening significantly improves in hypocontracting segments and returns to normal in hyperkinetic segments. In addition, our results suggest that the intraoperative echocardiographic semiquantitative measurement of percent of systolic wall thickening is less subjective than the determination of SWM as an index of left ventricular function immediately after CABG surgery.

References

1. Dubroff JM, Clark MB, Wong CYH, Spotnitz AJ, Collins RH, Spotnitz HM. Left ventricular ejection fraction during cardiac surgery: a two-dimensional echocardiographic study. Circulation 1983;68:95–103.
2. Topol EJ, Weiss JL, Guzman PA, et al. Immediate improvement of dysfunctional myocardial segments after coronary revascularization: detection by intraoperative transesophageal echocardiography. J Am Coll Cardiol 1984;4:1123–34.
3. Ren J-F, Panidis IP, Kotler MN, Mintz GS, Goel I, Ross J. Effect of coronary bypass surgery and valve replacement on left ventricular function: assessment by intraoperative two-dimensional echocardiography. Am Heart J 1985;109:281–9.
4. Koolen JJ, Visser CA, van Wezel HB, Meyne NG, Dunning AJ. Influence of coronary artery bypass surgery on regional left ventricular wall motion: an intraoperative two-dimensional transesophageal echocardiographic study. J Cardiothorac Anesth 1987;1:276–83.
5. Lazar HL, Plehn JF, Schick EM, Dobnic D, Shemin RJ. Effects of coronary revascularization on regional wall motion. An intraoperative two-dimensional echocardiographic study. J Thorac Cardiovasc Surg 1989;98:498–505.
6. London MJ, Tubau JF, Wong MG, et al. The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. Anesthesiology 1990;73:644–55.
7. Clements FM, de Bruijn NP. Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 1987;66:249–61.
8. Buffington CW, Coyle RJ. Altered load dependence of postischemic myocardium. Anesthesiology 1991;75:464–74.
9. Lowenstein E, Haering JM, Douglas PS. Acute ventricular wall motion heterogeneity: a valuable but imperfect index of myocardial ischemia. Anesthesiology 1991;75:385–7.
10. Edwards WD, Tajik AL, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. Mayo Clin Proc 1981;56:479–97.
11. Schnittger I, Fitzgerald PJ, Gordon EP, Alderman EL, Popp RL. Computerized quantitative analysis of left ventricular wall motion by two-dimensional echocardiography. Circulation 1984;70:242–54.
12. Parisi SF, Moynihan PF, Folland ED, Feldman CL. Quantitative detection of regional left ventricular contraction abnormalities by two-dimensional echocardiography. Circulation 1987; 63:761–7.
13. Mancini GBJ, DeBoe SF, Anselmo E, Simon SB, LeFree MT, Vogel RA. Quantitative regional curvature analysis: an application of shape determination for the assessment of segmental left ventricular function in man. Am Heart J 1987;113:326–34.
14. Cahalan MK, Ionescu P, Melton H. Automated real-time analysis of transesophageal echocardiograms (abstract). Anesthesiology 1991;75:A385.
15. Henry WL, De Maria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-Dimensional Echocardiography. Circulation 1980;62:212–7.
16. Cahalan MK, Lurz FC, Schiller NB. Transesophageal two-dimensional echocardiographic evaluation of anaesthetic effects on left ventricular function. Br J Anaesth 1988;60:99S–106S.
17. Abel MK, Nishimura RA, Callahan MJ, Rehder K, Ilstrup DM, Tajik AJ. Evaluation of intraoperative transesophageal two-dimensional echocardiography. Anesthesiology 1987;66:64–8.
18. Tennant R, Wiggers CJ. The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935;112:351–61.
19. Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF. Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978;234: H653–9.
20. Lieberman AN, Weiss JL, Jugdutt BI, et al. Two-dimensional echocardiography and infarct size: relationship of regional wall

motion and thickening to the extent of myocardial infarction in the dog. Circulation 1981;63:739–46.
21. Kerber RE, Martins JB, Marcus ML. Effect of acute ischemia, nitroglycerin and nitroprusside on regional myocardial thickening, stress and perfusion. Experimental echocardiographic studies. Circulation 1979;60:121–9.
22. Banka VS, Helfant RH. Temporal sequence of dynamic contractile characteristics in ischemic and nonischemic myocardium after acute coronary ligation. Am J Cardiol 1974;34:158–63.
23. Maniet AR, Banka VS. Echocardiographic monitoring during PTCA. Validation of the method (abstract). J Am Soc Echocardiogr 1990;3:226.
24. Kumar A, Minagoe S, Anthony P, Chandraratna N. Two-dimensional echocardiographic demonstration of restoration of normal wall motion after acute myocardial infarction. Am J Cardiol 1986;57:1232–5.
25. Saada M, Duval A-M, Bonnet F, et al. Abnormalities in myocardial segmental wall motion during lumbar epidural anesthesia. Anesthesiology 1989;71:26–32.
26. Force T, Kemper A, Perkins L, Gilfoil M, Cohen C, Parisi AF. Overestimation of infarct size by quantitative two-dimensional echocardiography. The role of tethering and of analytic procedures. Circulation 1986;73:1360–8.
27. Lehmann KG, Lee FA, McKenzie WB, et al. Onset of altered intraventricular septal motion during cardiac surgery. Assessment by continuous intraoperative transesophageal echocardiography. Circulation 1990;82:1325–34.

Continuous Endobronchial Insufflation During Internal Mammary Artery Harvest

Robert J. N. Watson, MB, BChir, FFARCS, Richard Szarko, MD, Colin F. Mackenzie, MB, ChB, FFARCS, Alejandro J. Sequeira, MD, and George M. Barnas, PhD

Departments of Anesthesiology, Surgery, and Physiology, University of Maryland School of Medicine, Baltimore, Maryland

Endobronchial insufflation of oxygen offers possible advantages over conventional ventilation modes in some clinical situations in which nonmovement of the chest may be desirable; however, endobronchial insufflation of oxygen has yet to be used during thoracic surgery in humans. Furthermore, the physiologic mechanisms underlying gas exchange during endobronchial insufflation of oxygen are unclear. This study assessed endobronchial insufflation of oxygen at 45 L/min in 11 patients with an open chest during internal mammary artery harvest. Cardiorespiratory function was measured at baseline during conventional mechanical ventilation and at 5-min intervals during the study period of 20–30 min. In all patients, clinically acceptable gas exchange was achieved, although $Paco_2$ increased from 32 ± 3.2 to 44 ± 7.5 mm Hg (mean ± SD) at 5 min, but thereafter was unchanged ($P > 0.1$). Cardiac output, vascular pressures, and heart rate were unchanged, although pHa decreased. Surgical access for internal mammary artery harvesting was improved. No mucosal damage or complications occurred. During endobronchial insufflation of oxygen, efficacy of gas exchange and body weight were not correlated, but both subject height and age were correlated with high Pao_2 and low $Paco_2$. We conclude that (a) endobronchial insufflation of oxygen can be used in patients with an open chest; (b) the efficacy of endobronchial insufflation of oxygen is probably improved by increased lung size and by collateral ventilation; and (c) cardiogenic gas mixing contributes little to gas exchange during endobronchial insufflation of oxygen.

(Anesth Analg 1992;75:219–25)

Continuous endobronchial insufflation of oxygen at total gas flow rates of 1 $L \cdot kg^{-1} \cdot min^{-1}$, delivered 2–3 cm beyond the carina into the left and right main bronchi, provides adequate oxygenation and carbon dioxide excretion in animals for several hours (1,2). In closed-chest humans, previous studies of endobronchial insufflation of oxygen at flow rates from 0.5 to 1.6 $L \cdot kg^{-1} \cdot min^{-1}$ have failed to demonstrate consistently acceptable carbon dioxide removal, and the cause of the variable success of the technique as applied to humans remains unexplained (3–5). There has been no attempt to correlate such factors as age, body weight, height, or presence of pathology with the efficacy of endobronchial insufflation of oxygen. Perhaps such correlations will help to determine the clinical utility of this technique and to provide insight into the mechanisms that contribute to gas mixing during continuous-flow ventilation.

Although endobronchial insufflation of oxygen has been used successfully in poststernotomy dogs (6,7), ventilation in humans with an open chest has not yet been attempted. Such use of endobronchial insufflation of oxygen may be especially valuable in clinical situations where lung distention and motion are undesirable. For example, during internal mammary artery harvesting for coronary artery bypass grafting, the sternum is widely retracted, and the pericardium is open. Lung inflation with conventional mechanical ventilation (CMV) intermittently impairs surgical access, and alternative ventilatory techniques such as one-lung ventilation to limit this interference can result in decreased gas exchange. Endobronchial insufflation of oxygen, in this situation, could potentially benefit the patient by improving the access and speed of internal mammary artery harvesting. The open-chest human is also an important model for understanding how endobronchial insufflation of oxygen works. The effect of cardiogenic gas mixing

Accepted for publication April 17, 1992.

Address correspondence to Dr. Watson, Department of Anesthesiology, University of Maryland Medical Center, Baltimore, MD 21201.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Clinical Characteristics of 11 Male Subjects Scheduled for Elective Coronary Artery Bypass Grafting With Internal Mammary Artery Harvesting

Pt No.	Age (yr)	Weight (kg)	Height (cm)	Left ventricular function	Smoking history
1	74	83	180	Mildly impaired	No
2	68	58	165	Normal	No
3	57	108	170	Normal	No
4	54	100	178	Mildly impaired	No (d/c 10 yr)
5	54	66	172	Normal	Yes (100 pk yr)
6	70	95	167	Normal	No (d/c 20 yr)
7	60	100	183	Within normal limits	No (d/c 15 yr)
8	67	97	193	Mildly impaired	No (d/c 5 yr)
9	63	51	185	Normal	No
10	71	68	167	Normal	Yes (70 pk yr), abuse
11	48	135	193	Moderately impaired	No (d/c 17 yr)

Pt, patient; d/c, discontinued after; pk yr, pack-years.

caused by mechanical deformation of the lung surfaces by the beating heart is thought to be important in continuous-flow techniques (6,7). Because the lungs are not opposed to the heart during internal mammary artery harvesting, cardiogenic oscillations should not contribute to gas mixing. If endobronchial insufflation of oxygen maintains gas exchange in this situation, then alternative mechanisms need to be considered.

We therefore studied patients during internal mammary artery harvesting to determine the effect of endobronchial insufflation of oxygen on surgical access. We also present initial data on the correlation between gas exchange and some physiologic variables. From these data we suggest some of the factors that may affect the success of gas exchange during endobronchial insufflation of oxygen.

Methods

After Institutional Review Board approval and patient consent, 11 male patients (87 ± 24.9 kg [mean ± SD], aged 62 ± 8.4 yr) scheduled for elective coronary artery bypass grafting with internal mammary artery harvesting were studied. Two of the patients were active cigarette smokers (Table 1). After premedication with morphine sulfate (0.15 mg/kg) and scopolamine (0.2–0.4 mg) intramuscularly, the patients breathed nasal oxygen during placement of two 14-gauge intravenous cannulas, a right radial artery catheter and a triple-lumen thermistor-tipped oximetric pulmonary artery catheter percutaneously through the right internal jugular vein under local anesthesia.

Anesthesia was induced with fentanyl (25–50 μg/kg IV) and midazolam (0.04–0.06 mg/kg IV). Vecuronium (0.1–0.2 mg/kg IV) was administered, and maintenance vecuronium requirements were monitored by peripheral nerve stimulator. The trachea was intubated with a catheter to be used for endobronchial insufflation of oxygen (Sheridan Catheter Corp., Argyle, N.Y.) that was placed outside a Hi-Lo jet endotracheal tube of 9.0-mm internal diameter (Mallinckrodt, Glens Falls, N.Y.). The insufflation catheter consisted of two 44-cm-long plastic tubes, each of 2-mm internal diameter and 2.7-mm outer diameter, which were bonded together for 30 cm of their length. The endobronchial portion consisted of 3-cm forked flexible ends that formed a 50° angle when unrestrained but could be held together for placement through the larynx. Positioning of the prongs astride the carina was performed in a blinded manner and subsequently checked by fiberoptic bronchoscopy after commencement of CMV through the cuffed tracheal tube. In all 11 patients, blind placement of the catheters was satisfactorily achieved. Other than during endobronchial insufflation of oxygen, the lungs were ventilated conventionally with 100% oxygen (Drager Narkomed II) at a rate of 8–10 breaths/min and tidal volume sufficient to maintain end-tidal CO_2 (monitored by Med Spec II, Allegheny International, St. Louis, Mo.) between 30 and 38 mm Hg. Body temperature was measured in the pulmonary artery. Arterial and mixed venous oxygen saturations were continuously monitored by a pulse oximeter (Nellcor, Hayward, Calif.) placed on the finger and by fiberoptic oximetry in the pulmonary artery, respectively. A five-lead electrocardiograph and continuous three-lead ST segment analysis were displayed together with systemic and pulmonary arterial pressures and central venous pressure waveforms on a Marquette series 7010 physiologic monitor.

The endobronchial insufflation delivery system (see Figure 1) utilized wall oxygen (50 psi) that was regulated to achieve a flow rate of 45 L/min at approximately 10 psi and passed through a calibrated rotameter before entering an active humidifier with a

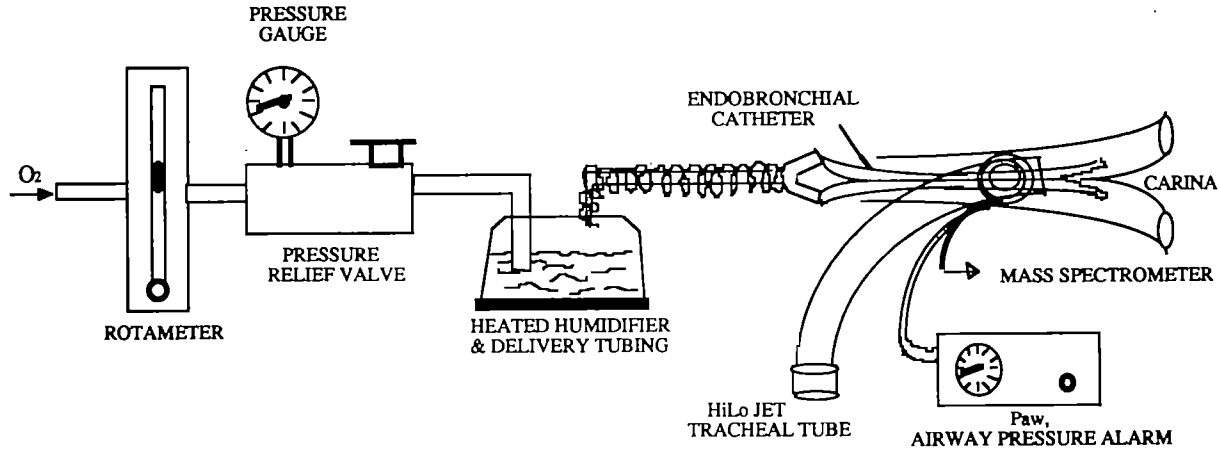


Figure 1. Diagram of the apparatus used for continuous endobronchial insufflation of oxygen.

heated-wire high-pressure delivery tube (Fisher-Paykel Dual Servo Model MR370). Overpressure protection of the system occurred at 15 psi. An independent aneroid airway pressure gauge and alarm connected to a dedicated lumen of the Hi-Lo tube continuously monitored and displayed tracheal airway pressure (Paw). The function of this system was checked before commencement and at regular intervals during operation. Additionally, the lungs were monitored closely by both the surgeon and one of the investigators to ensure that they remained deflated.

Full sets of measurements made before and during endobronchial insufflation of oxygen included intravascular pressures, heart rate, arterial and mixed venous blood gas tensions and pHa (blood sampled simultaneously and analyzed with temperature correction by Nova Stat Profile 5 multicomponent analyzer, Waltham, Mass.), end-tidal CO_2, and cardiac output by thermodilution. The first measurements were made during CMV after all variables were steady with an open chest (median sternotomy) and open pericardium. The CMV was then disconnected and endobronchial insufflation of oxygen was started with humidified, heated oxygen at a constant flow of 45 L/min, half going to each lung. Continuous exhalation to atmosphere occurred through the cuffed tracheal tube, and carbon dioxide tension was intermittently monitored by the multiplexing mass spectrometer. After starting endobronchial insufflation with oxygen, the internal mammary artery harvesting was carried out for 20–30 min. The Paw and arterial and mixed venous oxygen saturations were continuously monitored during this time, while measurements were repeated serially every 5 min. In all but 2 of the 11 patients, the procedure was carried out by the same senior surgeon who was in each case then asked to grade the surgical access.

Fiberoptic bronchoscopy was repeated after completion of the study, usually when the patient was on cardiopulmonary bypass. Correct position of the insufflation catheter was confirmed, and the mucosa was examined for evidence of damage before catheter removal. The patients were evaluated at extubation and at discharge from the intensive care unit for respiratory system complications. Statistical analysis used the paired *t*-test and a multivariate regression analysis designed to deal with clustered data (i.e., the dependence of repeated measurements within an individual subject) (8). We used a stepwise procedure to test the significance of the effects of age, height, weight, and time during endobronchial insufflation on $Paco_2$ and Pao_2. Values are expressed as mean ± SD; $P < 0.05$ was considered significant.

Results

All patients received at least 20 min of endobronchial insufflation of oxygen, during which internal mammary artery harvesting took place. In five patients, surgical considerations allowed us to extend insufflation to 25 min. In no patient was insufflation curtailed before completion of internal mammary artery harvesting. In all patients, the principal surgeon judged that access for the internal mammary artery harvesting was substantially improved by endobronchial insufflation of oxygen, compared with CMV. The lungs remained in a deflated state throughout endobronchial insufflation of oxygen, although on palpation they were felt to vibrate. The Paw remained at zero in all patients except two, in whom values of 1 and 2 cm H_2O were recorded.

Values for Pao_2 and $Paco_2$ are shown for individual patients in Figure 2. Mean (±1 SD) changes from baseline Pao_2 and $Paco_2$ are shown in Figure 3. The Pao_2 was unchanged from baseline throughout endobronchial insufflation of oxygen ($P > 0.5$) and re-

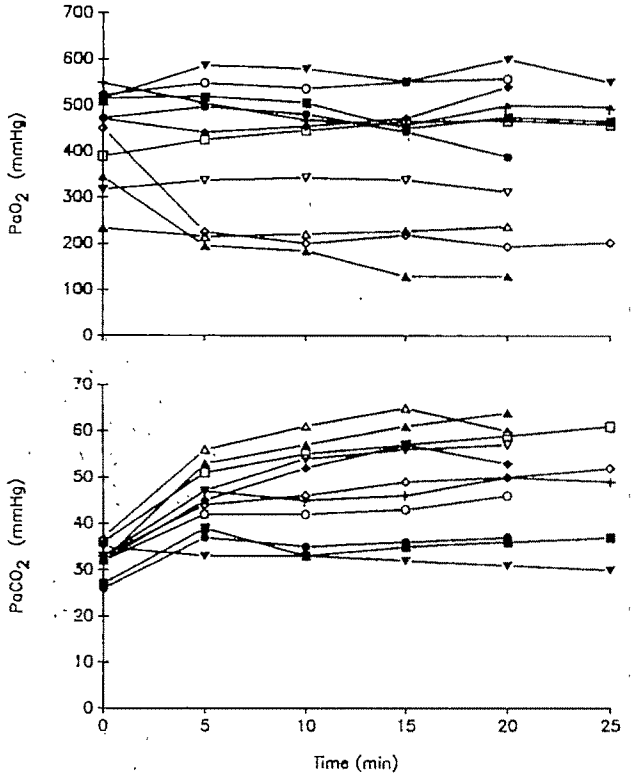


Figure 2. Individual subject Pao_2 and $Paco_2$ during conventional mechanical ventilation at time = 0 and during 45 L/min endobronchial insufflation of oxygen; time = 5–25 min.

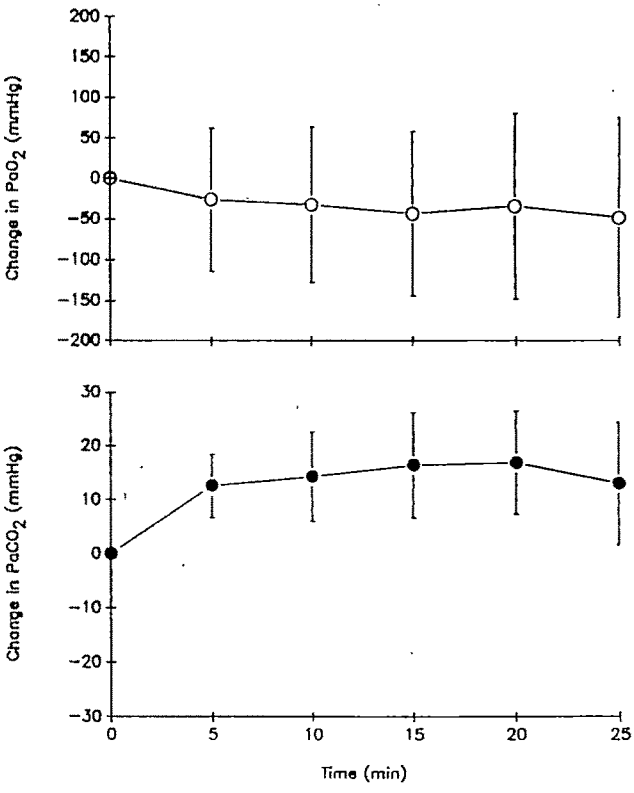


Figure 3. Change in Pao_2 and $Paco_2$ from baseline conventional mechanical ventilation value. Mean ± SD; n = 11 for time = 0–20 min; n = 5 for time = 25 min.

mained >200 mm Hg in all but one patient. The $Paco_2$ increased significantly during the first 5 min of endobronchial insufflation of oxygen, from 32 ± 3.2 to 44 ± 7.5 mm Hg. Thereafter, the $Paco_2$ was unchanged ($P > 0.1$). In three patients, $Paco_2$ was <38 mm Hg throughout 25 min of endobronchial insufflation of oxygen. In patient 8 (97 kg), the $Paco_2$ decreased at each measurement point during endobronchial insufflation of oxygen, compared with CMV.

Multivariate regression analysis showed that body weight had no effect on either Pao_2 or $Paco_2$ during endobronchial insufflation of oxygen at 45 L/min. There was, however, a significant correlation ($P < 0.01$) between age and Pao_2 and an inverse relationship between age and $Paco_2$ ($P < 0.01$). Body height showed significant correlation ($P < 0.05$) with high Pao_2 and low $Paco_2$ during endobronchial insufflation of oxygen. The overall correlation coefficients for the effects of age and height were 0.53 for Pao_2 and 0.69 for $Paco_2$ ($n = 61$).

Physiologic variables are shown in Table 2. There were no significant changes in intravascular pressures, heart rate, cardiac output, and systemic and pulmonary vascular resistance throughout and after 20 min of endobronchial insufflation of oxygen; however, the systemic pressure decreased slightly, whereas pulmonary artery pressure increased from 17.8 to 21 mm Hg. Arterial and venous pH decreased and venous Pco_2 increased significantly after 20 min of endobronchial insufflation of oxygen.

Fiberoptic bronchoscopy confirmed satisfactory cannula placement both before beginning and after ending endobronchial insufflation of oxygen in each patient. In no case was there evidence of laryngeal, tracheal, or bronchial damage, and no patient had any respiratory or other complications ascribed to the technique either during the procedure or after recovery from anesthesia and surgery.

Discussion

The present study reports results in the largest published group of patients to have received endobronchial insufflation of oxygen and the first group in which clinical benefit was derived from the technique. Gas exchange was acceptable in all patients, and there were no untoward cardiovascular events or complications from the procedure. On average, oxygenation remained unchanged from baseline values, and $Paco_2$ remained stable. In general, the patients with the best oxygenation also maintained low $Paco_2$,

Table 2. Physiologic Variables During Conventional Mechanical Ventilation and Endobronchial Insufflation of Oxygen in 11 Patients

Variable	During CMV	After 20 min of EIO (45 L/min)
$P\bar{v}o_2$ (mm Hg)	48 ± 2.4	55 ± 2.7
$P\bar{v}co_2$ (mm Hg)	40 ± 0.7	51 ± 3.3[a]
$pH\bar{v}$	7.4 ± 0.02	7.3 ± 0.03[a]
pHa	7.5 ± 0.01	7.3 ± 0.02[a]
$\dot{Q}s/\dot{Q}t$ (%)	19 ± 1.7	23 ± 3.6
$Ca-C\bar{v}Do_2$ (mL/min)	3.5 ± 0.32	3.1 ± 0.15
$\dot{V}o_2$ (mL/min)	174 ± 25.9	152 ± 12.8
$\dot{Q}t$ (L/min)	4.8 ± 0.4	5.0 ± 0.6
HR (beats/min)	71.3 ± 14.1	72.2 ± 17.4
MAP (mm Hg)	93.9 ± 14.0	83.9 ± 5.0
PAP (mm Hg)	17.8 ± 4.8	21 ± 4.4
SVR ($dyne \cdot cm^{-5} \cdot s^{-1}$)	1488 ± 150.0	1235 ± 127.8
PVR ($dyne \cdot cm^{-5} \cdot s^{-1}$)	100 ± 31.8	132 ± 36.3
Temp (°C)	35.8 ± 0.6	35.6 ± 0.6

CMV, conventional mechanical ventilation; EIO, endobronchial insufflation of oxygen; $P\bar{v}o_2$, mean mixed venous oxygen tension; $P\bar{v}co_2$, mean mixed venous carbon dioxide tension; $pH\bar{v}$, mixed venous pH; pHa, arterial pH; $\dot{Q}s/\dot{Q}t$, percent arteriovenous shunt; $Ca-C\bar{v}Do_2$, arteriovenous oxygen content difference; $\dot{V}o_2$, total body oxygen consumption; $\dot{Q}t$, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAP, mean pulmonary artery pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Temp, core body temperature.

Results are expressed as mean ± SD (n = 11).

[a]Significant at $P < 0.05$.

whereas those with poor oxygenation had high $Paco_2$; however, the two active smokers in the study (patients 5 and 10) also had high $Paco_2$ despite excellent oxygenation, whereas patient 2 maintained a stable $Paco_2$ of <38 mm Hg but had a deterioration in Pao_2.

Previous human studies of endobronchial continuous-flow ventilation have all been in closed-chest subjects. Comroe and Dripps (9) used tracheal insufflation of oxygen at 6–11 L/min in two patients. In one, the $Paco_2$ increased to 314 mm Hg after 3 h. More recently, Breen et al. (4) examined endobronchial insufflation of a 50% O_2/50% N_2O mixture in five patients at 60–120 L/min (0.9–1.6 $L \cdot kg^{-1} \cdot min^{-1}$) through 2.5–3.5-mm-internal diameter tubes fastened outside an orotracheal tube. The $Paco_2$ increased to 69 ± 14.5 mm Hg and Pao_2 varied between 100 and 240 mm Hg. The Paw was high, averaging 9 cm H_2O, and in three of the five patients, endobronchial insufflation was stopped after 5–20 min because of high Paw, high $Paco_2$, or low Pao_2. Perl et al. (5) reported endobronchial insufflation of oxygen at a flow rate of 26–38 L/min (0.5 $L \cdot kg^{-1} \cdot min^{-1}$) delivered through 1.2-mm-internal diameter tubes fastened inside a Carlen's double-lumen tube and positioned at the main stem bronchial orifices in five male patients undergoing hepatobiliary surgery. After 8 min, the $Paco_2$ increased on average from 39 to 58 mm Hg with no change in Pao_2.

Endobronchial insufflation studies in animals have shown that endobronchial catheter positioning is critical to efficient carbon dioxide elimination (2). Continuous-flow ventilation can produce normal oxygenation and ventilation without respiratory movement when a total fresh gas flow of 1 $L \cdot kg^{-1} \cdot min^{-1}$ is delivered 2–3 cm down both main stem bronchi, but gas insufflation above the carina is much less effective. The conclusions of the previously described human studies are similar. Breen et al. (4) had less success with carbon dioxide elimination than our study, despite the use of much higher gas flow rates in patients who weighed 15 kg less. Perl et al. (5), using gas flow rates similar to those in our study, demonstrated inadequate ventilation. In both cases, the lack of success may be attributed in part to the endobronchial apparatus used, which placed the two insufflating catheters at or above the bronchial orifices and which also may have offered increased expiratory flow resistance.

In contrast to Breen et al. (4) and Perl et al. (5), Babinski et al. (3) used an endobronchial apparatus very similar to that used both in previous animal studies and in the present study. They insufflated oxygen at 32–38 L/min (0.6–0.7 $L \cdot kg^{-1} \cdot min^{-1}$) through paired catheters of 2.5-mm outer diameter placed 2 cm into each bronchus of five patients undergoing hysterectomy. The $Paco_2$ increased only 0.6 mm Hg/min to 54.9 ± 4.0 mm Hg after 30 min and, in one patient, no increase in $Paco_2$ occurred. The Pao_2 was 299 ± 37 mm Hg after 30 min.

The relationship among ventilation, endobronchial insufflation flow rates, and body weight has not been established either in animals or in humans, and no optimal flow rate has been determined. We therefore decided to use oxygen at 45 L/min for all patients as the maximal flow available at a voluntarily imposed 10-psi working pressure limit for the system. Despite a greater than twofold variation in weight-indexed flow rate among our subjects (0.33–0.78 $L \cdot min^{-1} \cdot kg^{-1}$), we found no correlation between gas exchange and body weight. This illustrates that unlike the relationship assumed in previous studies, flow rates should not be based solely on subject weight. This absence of correlation may be the result of confounding variables, such as lung volume and degree of obesity. We did find a positive correlation between subject height and efficacy of gas exchange. Height is strongly correlated with vital capacity and residual volume (10), and it may be that larger lung volumes promote gas mixing because of increased mean airway diameter.

Efficacy of gas exchange was also strongly correlated with subject age. This may be the result of the increases in functional residual capacity and residual volume associated with increasing age (10). Another

factor may be the decrease in collateral airway resistance seen with aging in animals and in humans (11–13). It is known that lack of collateral airways impairs gas exchange during endobronchial insufflation of oxygen (14). The patients in our study were considerably older, averaging 62.4 ± 8.4 yr, than those reported in previous human studies (Babinski et al. [3], average 40.3 yr; Breen et al. [4], average 25.2 ± 8.1 yr; Perl et al. [5], five patients, 42–65 yr), and this may have contributed to the improved carbon dioxide elimination seen in our study population.

The results of this study have implications for the mechanisms of gas exchange during continuous-flow ventilation. Cardiogenic oscillations have been considered an important mechanism in promoting gas mixture in the lungs (15), especially during constant flow ventilation (16–18). They have been postulated to be directly transmitted across the pericardium and lung parenchyma (19,20), because cardiogenic gas mixing remains unchanged when the pulmonary artery is occluded (20). One result of sternal retraction and pericardiectomy is to minimize direct contact between the heart and lungs, which should reduce or eliminate the contribution of cardiogenic oscillations to gas mixing. Because gas exchange was as good as or better than that shown in other studies in closed-chest humans, it appears that cardiogenic oscillations are an insignificant gas-mixing mechanism during endobronchial insufflation of oxygen in humans. The success of endobronchial insufflation of oxygen in these patients may therefore have depended on alternative mechanisms for promoting gas exchange. For example, it is thought that lung vibration induced by turbulent flow in the airways increases gas mixing during continuous-flow ventilation (21). In our study, vibration of the lung surface was palpable in all patients.

Our study endorses the conclusions of previous authors (3–5,22) that, because the lungs, rib cage, diaphragm, and abdomen remain stationary, endobronchial insufflation of oxygen may be of clinical benefit in certain situations, such as intrathoracic surgery or imaging procedures. In our study there was consistent improvement in surgical exposure. An alternative clinical avenue for endobronchial insufflation of oxygen is as a supplement to CMV in patients with respiratory failure, where high airway pressures and gas flows may exacerbate the lung injury. Gilbert et al. (23) used endobronchial insufflation of oxygen at 8 L/min during the expiratory phase of CMV in a 20-yr-old, 64-kg adult with respiratory distress syndrome after other forms of ventilation proved inadequate. With this combination, CMV tidal volumes and airway pressures could be greatly reduced. In situations where extracorporeal carbon dioxide removal is unavailable, application of some form of endobronchial insufflation of oxygen may make an important contribution to life support.

Some concern over the safety of endobronchial insufflation is appropriate. When continuous high-flow insufflation is used, inadvertent obstruction to expiratory gas flow could quickly have catastrophic results, such as pneumothorax and gas embolism. Furthermore, the method used in this, and in previous studies, to monitor Paw is not failsafe in that obstruction of the pressure-monitoring lumen could allow true Paw to increase undetected. In addition, there is some evidence (24) that significant pressure gradients may exist between the trachea and peripheral parts of the bronchial tree during endobronchial insufflation. In the present study, we were able to satisfy our own concerns for patient safety by direct observation of the lungs to confirm the direct Paw measurements and to rule out hyperinflation. For future closed-chest human studies, some alternative alarm system, such as a monitor of expiratory gas flow, is desirable. Although laryngeal and bronchial mucosal erosion during endobronchial insufflation must also be of concern, no evidence for this was found either in our study or in previous human studies (3–5). In animal models, up to 72 h of high-frequency jet ventilation (when gas velocities and shear rates exceed those of continous-flow techniques) using adequate gas humidification failed to produce discernible tracheobronchial mucosal damage by either light or electron microscopy (25,26), although when dry gas was used, tracheal mucosal damage was found.

Although we would not advocate routine clinical use of this somewhat labor-intensive ventilatory technique, we believe that the clinical results are promising enough to justify further research.

References

1. Lenhert BE, Oberdoster G, Slutsky AS. Constant-flow ventilation of apneic dogs. J Appl Physiol 1982;53:483–9.
2. Slutsky AS, Menon AS. Catheter position and blood gases during constant-flow ventilation. J Appl Physiol 1987;62:513–51.
3. Babinski MF, Sierra OG, Smith RB, Leano E, Chavez A, Castellanos A. Clinical application of continuous flow apneic ventilation. Acta Anaesthesiol Scand 1985;29:750–2.
4. Breen PH, Sznajder JI, Morrison P, Hatch D, Wood LDH, Craig DB. Constant flow ventilation in anesthetized patients. Efficacy and safety. Anesth Analg 1986;65:1161–9.
5. Perl A, Whitwam JG, Chakrabarti MK, Taylor VM. Continuous flow ventilation without respiratory movement in cat, dog and human. Br J Anaesth 1986;58:544–50.
6. Babinski MF, Smith RB, Bunegin L. Continuous-flow apneic ventilation during thoracotomy. Anesthesiology 1986;65:399–404.
7. Mackenzie CF, Moorman RC, Smith J, Gundry S, Coughlin T, Hankins J. Gas mixing during apnea and continuous flow ventilation at low lung volumes (abstract). Anesthesiology 1987;67:A540.

8. Barnas GM, Mills PJ, Mackenzie CF, et al. Dependencies of respiratory system resistance and elastance on amplitude and frequency in the normal range of breathing. Am Rev Respir Dis 1991;143:240–4.
9. Comroe JH, Dripps RD. Artificial respiration. JAMA 1946;130: 381–3.
10. Agostini E, Hyatt RE. Static behavior of the respiratory system. In: Fishman AP, Macklem PT, Mead J, Geiger SR, eds. Handbook of physiology. Section 3, Volume 3, Part 1. Bethesda, Maryland: American Physiological Society, 1986:113–30.
11. Terry PB, Menkes HA, Traystman RJ. Effects of maturation and aging on collateral ventilation in sheep. J Appl Physiol 1987;62:1028–32.
12. Woolcock AJ, Macklem PT. Mechanical factors influencing collateral ventilation in human, dog, and pig lungs. J Appl Physiol 1971;30:99–115.
13. Rosenberg DE, Lyons HA. Collateral ventilation in excised human lungs. Respiration 1979;37:125–34.
14. Webster P, Menon AS, Slutsky AJ. Constant-flow ventilation in pigs. J Appl Physiol 1986;61:2238–41.
15. West JB, Hugh-Jones P. Pulsatile gas flow in bronchi caused by the heart beat. J Appl Physiol 1961;16:697–702.
16. Slutsky AS. Gas mixing by cardiogenic oscillations: a theoretical quantitative analysis. J Appl Physiol 1981;51:1287–93.
17. Cybutsky IJ, Abel JG, Menon AS, Salerno TA, Lichtenstein SV, Slutsky AS. Contribution of cardiogenic oscillations to gas exchange in constant-flow ventilation. J Appl Physiol 1987;63: 564–70.
18. Burwen DR, Watson J, Brown R, Josa M, Slutsky AS. Effects of cardiogenic oscillations on gas mixing during tracheal insufflation of oxygen. J Appl Physiol 1986;60:965–71.
19. Engel LA, Menkes H, Wood LDH, Utz G, Joubert J, Macklem PT. Gas mixing during breath holding studied by intrapulmonary gas sampling. J Appl Physiol 1973;35:9–17.
20. Mackenzie CF, Skacel M, Barnas GM, Brampton WJ, Alana CA. Effects of cardiac oscillations and lung volume on acinar gas mixing during apnea. J Appl Physiol 1990;68:2013–8.
21. Bitterman H, Kerem DH, Shabtal Y, Gavriely N, Palte T. Respiration maintained by externally applied vibration and tracheal insufflation in the cat. Anesth Analg 1983;62:33–8.
22. Mackenzie CF, Barnas GM, Smalley J, Moorman R, Baptiste J. Low-flow endobronchial insufflation with air for 2 hours of apnea provides ventilation adequate for survival. Anesth Analg 1990;71:279–84.
23. Gilbert J, Bunegin L, Larsson A, et al. Intermittent flow expiratory ventilation: new technique of limited excursion pulmonary ventilation. Crit Care Med 1991;19:1086–9.
24. Schumacker PT, Solway J, Wood LDH, Sznajder JI. Lobar contribution to $\dot{V}a/\dot{Q}$ inequality during constant-flow ventilation. J Appl Physiol 1988;65:2132–7.
25. Keszler M, Klein R, McClellan L, Nelson D, Platt M. Effects of conventional and high frequency jet ventilation on lung parenchyma. Crit Care Med 1982;10:514–6.
26. Doyle HJ, Napolitano AE, Lippman HR, et al. Different humidification systems for high-frequency jet ventilation. Crit Care Med 1984;12:815–9.

NEUROSURGICAL ANESTHESIA
Section Editor
Donald S. Prough

Modification of a New Catheter for Air Retrieval and Resuscitation From Lethal Venous Air Embolism: Effect of Nitrous Oxide on Air Retrieval

Alan A. Artru, MD

Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington

A modification of a new Arrow prototype catheter was evaluated for its ability to retrieve venous air emboli and for its effect on the success rate of resuscitation from venous air emboli in dogs anesthetized with isoflurane and nitrous oxide (66%) in oxygen. In an additional group of dogs, nitrogen was substituted for nitrous oxide in the inspired gases to determine whether the presence of nitrous oxide (as traditionally used in this model of lethal venous air emboli) increased the apparent amount of gas retrieval or altered the success rate of resuscitation. Dogs were placed in the seated position with the head 90° to the horizontal. The modified Arrow prototype catheter was placed with the proximal orifice just above the superior vena cava-right atrial junction and the distal orifice near the mid-right atrium. Dogs were then given a predetermined lethal dose of air (5 mL/kg) over 30 s through the jugular vein. Attempts to aspirate venous air emboli were begun with the first decrease in expired CO_2. The amounts of gas retrieved, expressed as a percent of the injected air, and the incidence of successful resuscitation were compared between groups. In both treatment groups (nitrous oxide and nitrogen), the percent of injected venous air retrieved (73% ± 13% and 65% ± 21%, mean value ± SD, respectively) and success rate of resuscitation (four of six dogs in each group) were significantly increased compared with the control group in which no attempt was made to retrieve injected venous air, and none of the six dogs survived. The success rate of resuscitation and percent of injected air retrieved (expressed as either that for all dogs or that for only survivors) in dogs receiving nitrous oxide were not significantly different compared with dogs receiving nitrogen. It is concluded that this modification of the Arrow prototype catheter is effective for aspiration of venous air and for resuscitation of dogs placed in the seated position and that the presence of nitrous oxide in the inspired gases does not affect the results in this model.

(Anesth Analg 1992;75:226–31)

Recently Noel (1) described a case in which a newly developed catheter prototype was used to retrieve 35 mL of air after the occurrence of a life-threatening venous air embolism (VAE) during a sitting craniotomy. The catheter prototype (Arrow International, Reading, Pa.) was 70 cm in length, with a balloon tip, end hole, and eight side holes. In previous studies (2–4) from this laboratory, the percent of VAE retrieval and the success rate of resuscitation from VAE were determined in dogs for a variety of catheters and sheaths: a single-orifice Sorensen CVP kit catheter, an American Edwards 7F Swan-Ganz catheter, a Cook Bunegin-Albin multiorifice catheter, Cook single- and multiorifice pulmonary artery catheter introducer sheaths, and an Arrow Antecubital Central Venous catheter. There are no laboratory studies reporting the percent of VAE retrieval and the success rate of resuscitation from VAE with the new Arrow prototype catheter. One purpose of the present study was to examine the efficacy of a modified version of the new Arrow prototype catheter in a model that would permit comparison with the previously studied catheters and sheaths.

In previous studies from this laboratory, dogs were anesthetized with 0.5% isoflurane and 66% nitrous oxide (N_2O) in oxygen during VAE. Consequently, N_2O may have contributed to the gas retrieval from catheters or sheaths and therefore caused an overestimation of the percent of VAE retrieval with those catheters or sheaths. The second purpose of the present study was to determine whether the presence of N_2O in the inspired gases during lethal VAE in dogs alters the percent of VAE retrieved with

Accepted for publication March 31, 1992.

Address correspondence to Dr. Artru, Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, WA 98195.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

the modified version of the new Arrow prototype catheter.

Methods

The experimental protocol was similar to that used previously in this laboratory for studies of VAE in dogs (2–4). The study was approved by the Institutional Animal Care Committee. Eighteen dogs (weight 16–22 kg) were anesthetized with isoflurane (1.7% inspired) and N_2O (66%) in oxygen. The dogs' lungs were ventilated to maintain arterial O_2 tension (Pao_2) >120 mm Hg and arterial CO_2 tension ($Paco_2$) at 35–40 mm Hg. Expired CO_2 was continuously monitored with a Beckman LB-2 medical gas analyzer. An electronic offset was used to minimize interference by expired N_2O on the strip chart recorder display. The left jugular vein was cannulated for injection of air. The right jugular vein was cannulated with the Arrow prototype catheter for measurement of central venous pressure (CVP) and, where appropriate, retrieval of injected air (see following text). Because only 6% ± 2% of injected air was retrieved with the Arrow Antecubital Central Venous Catheter (four oval side orifices, each 1.0 × 1.5 mm in diameter, with the most proximal orifice placed approximately 3 cm from the tip [4]), the new Arrow prototype catheter (internal diameter approximately 1.8 mm) was modified by placing 10 oval side orifices (five on one "side" of the catheter and another five on the opposite "side"), each 1.0 × 1.5 mm in diameter, with the most distal orifice 1.5 cm from the tip and the most proximal 6.0 cm from the tip. The right femoral vein was cannulated for fluid administration. A femoral artery was cannulated for sampling of blood for gas analysis and for continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure was determined by electronic integration. Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 ± 0.5°C by heat lamp or ice packs. Vascular volume was maintained by continuous infusion of saline solution (4–6 $mL \cdot kg^{-1} \cdot min^{-1}$).

The dogs were turned to the prone position and the head slightly elevated and fixed in a stereotactic frame. A midsagittal scalp incision was made to expose the left calvarium; a burr hole was made over the left hemisphere; and a catheter was directed into the underlying ventricle for measurement of cerebrospinal fluid pressure. At the conclusion of the surgical preparation, wound edges were infiltrated with bupivacaine (0.5%), and the concentration of isoflurane was decreased to 0.5% (inspired, $\%N_2O$ unchanged).

The dogs were then seated on a chair and the head was fixed in a stereotactic frame so that the head and upper trunk were in the upright position (i.e., 90° to the horizontal). Up to 200 mL of saline solution was administered to achieve a CVP of approximately 2 mm Hg with the transducer zeroed at the top of the atrium. Once systemic variables had stabilized (25 min after decreasing isoflurane to 0.5%), baseline values for systemic variables were recorded. These included CVP, mean arterial pressure, cerebrospinal fluid pressure, heart rate, arterial blood gas tensions, arterial blood hemoglobin levels, and nasopharyngeal temperature.

The dogs were randomly assigned to one of three groups. In the first (control) group of six dogs, the modified Arrow prototype catheter was used to measure CVP but was not used to aspirate air. Inspired N_2O was continued at 66%. In the second group of six dogs, the modified Arrow prototype catheter was used to measure CVP and to aspirate air. Inspired N_2O was continued at 66%. In the third group of six dogs, N_2O was discontinued and replaced with nitrogen to achieve an inspired concentration of 66% in oxygen. As in the second group, the modified Arrow prototype catheter was used to measure CVP and to aspirate air. In all three groups, the modified Arrow prototype catheter was examined in a position close to that reported by Bunegin et al. (5) as optimal for aspirating air with a multiorifice catheter. The proximal orifice of the modified Arrow prototype catheter was placed approximately 2–3 cm above the junction of the superior vena cava (SVC) and right atrium (RA) and the distal orifice near the mid-RA (approximately 3–4 cm below the RA-SVC junction). The catheter was positioned by using it as an exploring electrocardiographic lead (6). The balloon at the catheter tip was not inflated during catheter placement.

The multiorifice portion of the catheter was advanced until the point of maximal negative P-wave deflection with no positive P-wave component. This point was taken to indicate that the multiorifice portion of the catheter was at the SVC-RA junction. The catheter was advanced 1–2 cm once the point of maximal P-wave deflection was reached. Because the proximal and distal orifices are approximately 6 cm apart, this maneuver placed the proximal orifice approximately 1–2 cm above the SVC-RA junction and the distal orifice near the mid-RA (6).

The dose of air chosen for injection in this study was 5 mL/kg. This dose was chosen based on previous reports (2–4) that 5 mL/kg, injected over 30 s, was the mean fatal VAE for dogs in both the prone and upright positions when doses of 3, 5, or 7 mL/kg air were administered intravenously. Resuscitation was not attempted in the control group but was attempted in the other two groups. The only method of resuscitation used was aspiration of VAE. Attempts to retrieve VAE were made with 50-mL syringes at-

Table 1. Systemic Values Before First Air Injection

	Control group (66% inspired N_2O) (n = 6)	Modified Arrow catheter groups	
		66% inspired N_2O (n = 6)	66% inspired nitrogen (n = 6)
Pao_2 (mm Hg)	138 ± 19	133 ± 15	137 ± 12
$Paco_2$ (mm Hg)	38 ± 2	38 ± 2	37 ± 3
pHa	7.34 ± 0.03	7.31 ± 0.01	7.31 ± 0.03
Bicarbonate (mEq/L)	19.4 ± 0.9	18.7 ± 1.4	18.4 ± 1.2
Hemoglobin (g/dL)	13.9 ± 1.6	14.9 ± 2.0	14.2 ± 1.7
MABP (mm Hg)	107 ± 18	112 ± 17	103 ± 11
CVP (mm Hg)	3 ± 1	2 ± 1	3 ± 1
CSF pressure, ventricular (cm H_2O)	10 ± 1	10 ± 1	11 ± 1
HR (beats/min)	106 ± 18	100 ± 23	112 ± 17
Temp, nasopharyngeal (°C)	37.2 ± 0.5	37.4 ± 0.5	37.1 ± 0.5

Pao_2, arterial O_2 tension; $Paco_2$, arterial CO_2 tension; MABP, mean arterial blood pressure; CVP, central venous pressure; CSF, cerebrospinal fluid; HR, heart rate. Temp, temperature.
Results are mean values ± SD.

tached to the catheter. Aspiration was begun as soon as expired CO_2 decreased after injection of air. The "plunger" of the 50-mL syringe was pulled back manually with as much force as could be generated by hand. The negative force generated during aspiration was not measured. Aspiration was continued until gas was no longer seen to be entering the syringe. In cases where large amounts of gas were retrieved, it was often necessary to use more than one 50-mL syringe. Invariably, blood was aspirated, but because the amount of blood was small (11–28 mL) and was not significantly different between groups, no attempt was made to reinfuse the aspirated blood.

Where dogs were successfully resuscitated from the first VAE, 30 min was allowed for cardiovascular stabilization; a second dose of 5 mL/kg of air was injected; and attempts were made to retrieve the VAE. This repeat VAE was designed to determine whether the modified Arrow prototype catheter remained as effective with a second VAE as with a first VAE and whether continued administration of N_2O (in the second group) decreased the likelihood of successful resuscitation from a second VAE. Where dogs were successfully resuscitated from the second VAE, 30 min was allowed for cardiovascular stabilization; a third 5 mL/kg of air was injected; and no attempt was made to retrieve the VAE. This third VAE was designed to determine whether the dogs that survived VAE when the catheter was used for resuscitation might also have survived had the catheter not been used.

The volume of gas retrieved was expressed as percent of injected air. The term gas is used because the retrieved gas was composed of both the injected air and whatever amount of N_2O (in the second group) might have diffused into the injected air. In the present study, the percent of injected air and systemic variables were compared between groups by analysis of variance. The incidence of successful resuscitation between groups and the percentage of VAE that was retrieved in survivors and nonsurvivors were compared by the variance ratio test (7). A P value <0.05 was considered statistically significant. Results are reported as mean values ± SD. Resistance of this modified version of the Arrow prototype catheter was determined, as reported in a previous study (4), by measuring the flow of H_2O at 10, 20, and 30 cm H_2O pressure for 1–2 min and expressing resistance as cm $H_2O \cdot mL^{-1} \cdot min$.

Results

There were no significant differences between groups with respect to systemic circulatory variables or blood chemistry before infusion of air (Table 1). The incidence of successful resuscitation from VAE was significantly greater with the Arrow catheter than in the control group (Table 2). Catheter resistance was 2.04 cm $H_2O \cdot mL^{-1} \cdot min$. With both the first and second injections of air, the amount of gas retrieved, the amount of blood retrieved, the percent of injected air retrieved, and the success rate of resuscitation when N_2O was continued in the inspired gases were not significantly different than when N_2O was replaced with nitrogen. Blood and gas retrieval and success of resuscitation in the N_2O group were also not significantly different from that in the nitrogen group when only the data from the dogs surviving the first injection of air were compared. In dogs surviving the first VAE, the amount of gas retrieved was 72 ± 17 mL, the amount of blood retrieved was 18 ± 6 mL, and the percent of inspired gas retrieved was 77% ± 12% when N_2O was continued in the

Table 2. Retrieval of Intravenously Injected Air and Success Rate of Resuscitation

	Control group (66% inspired N_2O) ($n = 6$)	Modified Arrow catheter groups	
		66% inspired N_2O ($n = 6$)	66% inspired nitrogen ($n = 6$)
First air injection			
Air injected (mL)	97.6 ± 8.1	91.3 ± 7.2	97.2 ± 8.9
No. of dogs	6	6	6
Gas retrieved (mL)	0	67.3 ± 15.7	62.7 ± 21.3
Blood retrieved (mL)	0	20.3 ± 5.6	20.3 ± 5.9
Injected air retrieved (%)	0	73.2 ± 13.4	65.0 ± 20.7
Surviving dogs (n)	0/6	4/6	4/6
Second air injection			
Air injected (mL)	—	92.8 ± 8.8	95.3 ± 10.8
No. of dogs	—	4	4
Gas retrieved (mL)	—	66.3 ± 10.2	69.5 ± 6.2
Blood retrieved (mL)	—	14.0 ± 4.5	14.5 ± 3.0
Injected air retrieved (%)	—	71.0 ± 5.4	73.3 ± 2.2
Surviving dogs (n)	—	4/4	4/4
Third air injection			
Amount of air injected (mL)	—	92.8 ± 8.8	95.3 ± 10.8
No. of dogs	—	4	4
Amount of gas retrieved (mL)	—	0	0
Surviving dogs (n)	—	0/4	0/4

Results are mean values ± SD.

inspired gases. When N_2O was replaced by nitrogen in the inspired gases, the amount of gas retrieved was 74 ± 15 mL, the amount of blood retrieved was 18 ± 6 mL, and the percent of inspired gas retrieved was 78% ± 8%.

With the first injection of air, the proportion of survivors where a "large" amount of injected air was retrieved (previously defined as >62% of injected air [2–4]) was 4/4 when N_2O was continued in the inspired gases and 4/4 when N_2O was replaced with nitrogen. In nonsurvivors, >62% of injected air was retrieved in one of two dogs with N_2O and none of two dogs with nitrogen. With the second injection of air, >62% of injected air was retrieved in four of four survivors with N_2O and four of four survivors with nitrogen.

Discussion

One principal finding of the present study was that the modification of the Arrow prototype catheter allowed retrieval of most of the dose of intravenously injected air and provided resuscitation from a lethal dose of venous air in most dogs. The percent of injected venous air retrieved (65% ± 21% to 73% ± 13%) was qualitatively similar to that previously reported with the Bunegin-Albin catheter (63% ± 14%, mean value ± SEM) and with Cook single- and multiorifice pulmonary artery (PA) catheter introducer sheaths (56% ± 24% and 79% ± 30%, respectively, mean values ± SD) in dogs in the seated position (3,4). The percent of injected venous air retrieved with the modified Arrow prototype was qualitatively greater than that previously reported when both ports (CVP and PA) of a PA catheter were aspirated simultaneously (14% ± 10% to 16% ± 18%, mean values ± SD) in dogs in the seated position (3,4). Gas retrieved with the modified Arrow prototype also was qualitatively greater than that previously reported when a Sorensen catheter was located in the SVC (16% ± 6%, mean value ± SEM) or the mid-RA (10% ± 3%) in dogs in the prone position (2).

The success rate of resuscitation with the modified Arrow prototype was qualitatively similar to that previously reported with the Bunegin-Albin catheter in seated dogs (four of six) and prone dogs (six of nine) (2,4). The success rate of resuscitation with the modified Arrow prototype was qualitatively greater than that previously reported with Cook single- and multiorifice PA catheter introducer sheaths (three of six and two of six dogs, respectively; not significantly different from control animals in that study), when a Sorensen catheter was located in the SVC or mid-RA (none of seven dogs in both groups; not significantly different from control animals in that study) (2,3), or when both ports of a PA catheter were aspirated simultaneously (one of six dogs in each of two studies; not significantly different from the respective control animals in each study) (3,4). It should be

noted that positioning and aspiration of the catheter in this study (distal orifice near mid-RA with use of intravascular electrocardiography) differed from that reported by Noel (1) (placement first in the PA and then withdrawal into the RA-SVC junction during VAE after gas was retrieved from the PA).

Another principal finding of the present study was that the presence of N_2O in the inspired gases during lethal VAE did not alter the percent of gas retrieved or the success rate of resuscitation. The percent of gas retrieved and success rate of resuscitation with 66% inspired N_2O in oxygen were not significantly different from that with 66% inspired nitrogen in oxygen for either the first intravenous injection of air or the second injection. With injection of a lethal dose of air over 30 s, expired CO_2 decreased, and catheter aspiration was begun within 30 s of completing the VAE injection. Thus, <60 s was available for passage of N_2O into the VAE. This period may not be sufficient for significant amounts of N_2O to enter VAE (8). In loops of stomach, small intestine, or colon irrigated with 20–120 mL of air, N_2O (70%–80% inspired in oxygen) increased the volume of gas by approximately 30% after approximately 30 min of exposure to N_2O. In a closed pneumothorax produced with 300 mL of air, N_2O (68%–78% inspired) increased the volume by 100% after 10 min of exposure to N_2O. In endotracheal tube cuffs inflated with air, N_2O increased the volume by 15%–70% after 60 min of exposure to N_2O. Thus, the maximal calculated increase in VAE volume in the present study resulting from inward diffusion of N_2O is approximately 7.5%,* whereas the minimal calculated increase in VAE is <1%.

The resistance of this modified version of the new Arrow prototype catheter (2.04 cm $H_2O \cdot mL^{-1} \cdot min$) was qualitatively greater than that previously reported with the Cook Bunegin-Albin multiorifice catheter (0.77 cm $H_2O \cdot mL^{-1} \cdot min$) and less than that previously reported with the Arrow Antecubital Central Venous catheter (5.75 cm $H_2O \cdot mL^{-1} \cdot min$) and the RA and PA ports of the American Edwards 7F Swan-Ganz catheter (8.70 and 10.20 cm $H_2O \cdot mL^{-1} \cdot min$) (4).

With regard to the experimental design of the present study, intravenous injection of a second dose of air after successful resuscitation from the first dose permitted assessment of the effectiveness of the Arrow prototype catheter for recurrence of VAE. In dogs breathing 66% nitrogen in oxygen, the similarity in percent of gas retrieved from survivors of the first VAE (78% ± 8%) and survivors of the second VAE (73% ± 2%) indicates that the Arrow prototype catheter remains useful for aspiration of air entering the heart by the SVC. In dogs breathing 66% N_2O in oxygen, the similarity in percent of gas retrieved from survivors of the first VAE (77% ± 12%) and survivors of the second VAE (71% ± 5%) indicates that the continued administration of N_2O after successful resuscitation from VAE does not decrease the usefulness of the Arrow prototype catheter for aspiration of air entering the heart by the SVC. In both groups, the percent of air retrieved after a second intravenous injection of air was similar to the percent of air retrieved with the Bunegin-Albin catheter after a second VAE in a previous study (76% ± 10%, author's unpublished data from previous study [4]). In the present study, the finding that all dogs successfully resuscitated from the first dose of intravenously injected air (four of four dogs in both the N_2O and nitrogen groups) were also successfully resuscitated from the second dose indicates that the Arrow prototype catheter remains effective for resuscitation from recurrence of VAE. This finding may also suggest that the catheter was in a better position in these dogs compared with those that did not survive. The finding that dogs surviving a second VAE when the Arrow prototype catheter was used to aspirate air did not survive a subsequent VAE when no attempt was made to aspirate air suggests that 5 mL/kg would have been a fatal dose of intravenous air for the N_2O and nitrogen groups, as well as for the control group.

In summary, in dogs in the seated position, a modification of a new Arrow prototype catheter permitted retrieval of large amounts of intravenously injected air and successful resuscitation from lethal VAE in 8 of 12 dogs. The effectiveness of this modified Arrow prototype catheter equaled that of the Bunegin-Albin catheter, previously reported to be the most effective catheter (among those approved for use in patients) for resuscitation in this model of VAE (2–4). The presence of N_2O in the inspired gases during lethal VAE did not increase the apparent percentage of VAE retrieved and did not decrease (or increase) the success rate of resuscitation from VAE compared with that in dogs breathing nitrogen in oxygen. The present results support further study of a modified form of this new Arrow prototype catheter for use in patients.

*Exposure of VAE during intravenous injection of air was estimated as the mean of no exposure (0 s) and exposure of full VAE to N_2O (30 s). Maximal time of exposure of VAE after injection was 30 s. Thus, estimated maximal exposure time (total) was approximately 45 s. Estimated maximal expansion rate (taken from previously published pneumothorax data) was 10%/min.

References

1. Noel TA II. Air embolism removal from both pulmonary artery and right atrium during sitting craniotomy using a new catheter: report of a case. Anesthesiology 1989;70:709–10.

2. Colley PS, Artru AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in dogs. Anesth Analg 1987;66:991–4.
3. Bowdle TA, Artru AA. Treatment of air embolism with a special pulmonary catheter introducer sheath in sitting dogs. Anesthesiology 1988;68:107–10.
4. Colley PS, Artru AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in upright dogs. Anesth Analg 1989;68:298–301.
5. Bunegin L, Albin MS, Helsel PE, Hoffman A, Hung TK. Positioning the right atrial catheter: a model for reappraisal. Anesthesiology 1981;55:343–8.
6. Artru AA, Colley PS. Site of origin of IVECG with multiorificed catheters. Anesthesiology 1988;69:44–8.
7. Ipsen J, Feigl P, eds. Bancroft's introduction to biostatistics. New York: Harper & Row, 1970:77–87.
8. Eger EI II, ed. Nitrous oxide. London: Edward Arnold, 1985;81–107.

Intracranial Pressure Effects of Dexmedetomidine in Rabbits

Mark H. Zornow, MD, Mark S. Scheller, MD, Patrick B. Sheehan, MD, Martin A. P. Strnat, MS, and Mishiya Matsumoto, MD

Department of Anesthesiology, University of California at San Diego, San Diego, California

The α_2-adrenergic receptor agonist dexmedetomidine produces an anesthetic state in a variety of species. Although its effects on cerebral blood flow and the electroencephalogram have been investigated, the effect of this drug on intracranial pressure (ICP) has not been reported previously. Dexmedetomidine therefore was intravenously administered to 24 New Zealand white rabbits that had been anesthetized with halothane and mechanically ventilated to maintain a constant arterial CO_2 tension ($Paco_2$) between 34 and 39 mm Hg. After placement of an arterial catheter and ventricular cannula, baseline measurements of monitored variables, including heart rate, mean arterial blood pressure, ICP, end-tidal CO_2, body temperature, and arterial blood gases, were recorded. Dexmedetomidine (20, 80, or 320 μg/kg IV) or saline solution was then infused over a 10-min period. The ICP transiently decreased by 31% in the 20-μg/kg group (from a mean value of 9.4 ± 1.3 [SEM] to 6.5 ± 1.0 mm Hg, $P < 0.05$). In the 320-μg/kg group, ICP remained unchanged over the course of the study despite a significant increase in arterial blood pressure (32 mm Hg). The effects of dexmedetomidine on ICP were next investigated in the presence of intracranial hypertension produced by a cryogenic lesion (mean baseline ICP 16.8 mm Hg). In addition to the previously monitored variables, sagittal sinus blood flow was measured by the hydrogen clearance technique before and after the administration of dexmedetomidine (320 μg/kg IV). In these experiments, dexmedetomidine was associated with a 14% decrease in sagittal sinus blood flow that was not statistically significant. There was no change in ICP after the administration of dexmedetomidine in this model of intracranial hypertension. From these studies, we conclude that dexmedetomidine has minimal effects on ICP in halothane-anesthetized rabbits.

(Anesth Analg 1992;75:232–7)

Dexmedetomidine is a potent and selective agonist of the α_2-adrenergic receptor (1,2). It has been shown to possess anestheticlike properties in a variety of species and to be capable of reducing volatile anesthetic requirements during surgery in humans (3,4). More recently, it has been shown to possess neuroprotective properties in an animal model of transient global ischemia (5). The potential to antagonize the anesthetic activity of dexmedetomidine with α_2-antagonists (e.g., idazoxan, atipamezole) (6) may make this drug useful during neurosurgical procedures where prompt awakening from anesthesia is often a desirable goal.

Previous studies (7,8) conducted in dogs have demonstrated that dexmedetomidine can decrease cerebral blood flow, presumably by α_2-adrenergic receptor-mediated vasoconstriction. These findings suggest that the administration of dexmedetomidine may decrease intracranial pressure (ICP) by decreasing cerebral blood volume. To investigate this possibility, we first examined the cerebral and hemodynamic effects of three different bolus doses of dexmedetomidine in halothane-anesthetized rabbits. Next, the effects of dexmedetomidine on cerebral blood flow and ICP were studied in a model of acute brain injury and preexisting intracranial hypertension produced by a cryogenic lesion.

Methods

Phase I: Dose-Range Study

Twenty-four New Zealand white rabbits weighing 2.5 ± 0.1 kg (mean ± SEM) were anesthetized with 4% halothane in a Plexiglas box. An ear vein catheter was inserted for the administration of maintenance fluids (0.9% saline solution at 4 $mL \cdot kg^{-1} \cdot h^{-1}$) and drugs. The animals' tracheas were intubated with a 3.0-mm internal diameter (ID) cuffed tube and mechanical ventilation was begun (rate of 25 breaths/min with

This work was supported in part by a gift from the Orion Corporation and by NIH NINDS Grant RO1-NS29403-01 (to M.H.Z.). Dr. Scheller is the recipient of the B. B. Sankey Anesthesia Advancement Award for 1991 from the International Anesthesia Research Society.

Accepted for publication March 31, 1992.

Address correspondence to Dr. Zornow, Neuroanesthesia Research 0629, UCSD, 9500 Gilman Drive, La Jolla, CA 92093.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

a tidal volume of 40 mL) with 1.5%–2.0% halothane in oxygen. Ventilation was subsequently adjusted on the basis of frequent arterial blood gas evaluation to maintain an arterial CO_2 tension ($Paco_2$) of 35–40 mm Hg. An esophageal temperature probe was used to servocontrol the animals' temperatures to 37°C through the use of heat lamps and a warming pad. After infiltration with 0.25% bupivacaine, a femoral arterial catheter was inserted for the continuous monitoring of arterial blood pressure and intermittent determination of arterial blood gases. Finally, the scalp was incised in the midline and reflected laterally to expose the surface of the skull. A 2-mm-diameter burr hole was drilled 8 mm lateral and 7 mm posterior to the bregma. A stereotactic manipulator was used to advance a ventriculostomy needle into the lateral ventricle for the measurement of ICP.

After completion of surgical preparation, the animals were randomly assigned to receive 20 ($n = 6$), 80 ($n = 6$), or 320 ($n = 6$) μg/kg IV of dexmedetomidine or an equal volume (7 mL) of saline solution ($n = 6$) by 10-min infusion. Monitored variables (arterial blood pressure, ICP, heart rate, arterial blood gases, temperature, and inspired halothane concentration) were recorded at 5 and 10 min ($t = -5$ and $t = -10$) before starting the dexmedetomidine infusion at $t = 0$ and then again at 1, 5, 10, 20, 30, and 40 min after the start of the infusion. Data were analyzed with two-way analysis of variance (ANOVA), followed by Dunnett's test to compare the values obtained for the saline solution group versus the dexmedetomidine groups at each of the measurement points. To examine the effects of an α_1- versus an α_2-adrenergic agonist on ICP in this experimental setting, an additional seven rabbits were prepared in the manner previously described. After recording of baseline values, phenylephrine was infused at rates sufficient to duplicate the changes in arterial blood pressure that were observed in the 320-μg/kg dexmedetomidine group.

Phase II: Acute Brain Injury Model

The 13 animals used in this portion of the study were anesthetized and surgically prepared in a manner identical to that used in phase I. In addition, a cryogenic lesion was created over the left hemisphere by cementing a funnel (mouth diameter 15 mm) to the skull. Liquid nitrogen was poured into this funnel for a period of 40 s. The funnel was then removed and the cortical freeze lesion allowed to mature for 1 h. During this time, a small craniotomy was performed to expose the confluence of sinuses. A platinum-iridium needle electrode was advanced into the sinus for measurement of cerebral blood flow using the hydrogen clearance technique (9–11). In a randomized fashion, dexmedetomidine (320 μg/kg) or an equal volume of saline solution was administered over a 5-min period. Monitored variables were recorded immediately before the dexmedetomidine infusion ($t = 0$) and at 1, 3, 5, 6, 7, 10, and 20 min after the start of the infusion. Cerebral blood flow data were obtained before the start of the drug infusion and after its completion. Data were analyzed using statistical methods similar to those described for the phase I study.

Results

Phase I

There were no significant differences among the various groups during the course of the study for pH, arterial O_2 tension (Pao_2), or $Paco_2$. The $Paco_2$ values ranged between 34 and 39 mm Hg (Table 1). Mean arterial blood pressure (MAP) decreased by approximately 20% in those animals that received 20 μg/kg of dexmedetomidine. In contrast, 80- and 320-μg/kg doses resulted in transient increases in arterial blood pressure, which returned to baseline or less within 15–20 min of completing the dexmedetomidine infusion (Figure 1). The MAP in the 80-μg/kg group was significantly decreased at $t = 30$ and $t = 40$ min compared with the saline solution group. Heart rate decreased in all drug-treated groups in a significant manner (Figure 2). The most profound bradycardia occurred in the 320-μg/kg group. Heart rate had started to return toward baseline values by completion of the study at $t = 40$ min. The ICP decreased significantly in the 20-μg/kg group at $t = 5$ and $t = 10$ min compared with preinfusion baseline values. There was no significant change in ICP in the 80- or 320-μg/kg groups (Figure 3). In those animals that received phenylephrine (mean total dose 93 ± 8 μg/kg), temporal changes in arterial blood pressure were similar to those produced by 320 μg/kg of dexmedetomidine. The ICP remained unchanged from baseline values throughout the phenylephrine infusion.

Phase II

One hour after the production of the cryogenic lesion, ICP had doubled to a mean of 16.8 mm Hg, but there was no difference between the dexmedetomidine (18 ± 4 mm Hg) and saline solution groups (16 ± 9 mm Hg). Subsequent infusion of 320 μg/kg of dexmedetomidine resulted in a prompt but transient elevation of MAP (from a baseline of 64 mm Hg to a peak of 109 mm Hg) (Figure 4), similar to that observed in the phase I study. There were no significant differences in ICP between the two groups at any time despite the abrupt and significant change in arterial blood pressure in the dexmedetomidine

Table 1. pH and Arterial Blood Gas Variables for Phase I of Study

	Study group	Baseline	t = 5 min	t = 40 min
pHa	Saline solution	7.39 ± 0.02	7.37 ± 0.01	7.35 ± 0.02
	Dexmedetomidine			
	20 μg/kg	7.39 ± 0.01	7.37 ± 0.02	7.38 ± 0.01
	80 μg/kg	7.45 ± 0.02	7.43 ± 0.02	7.43 ± 0.03
	320 μg/kg	7.40 ± 0.02	7.39 ± 0.02	7.39 ± 0.03
$Paco_2$ (mm Hg)	Saline solution	36.2 ± 0.7	37.5 ± 0.7	36.3 ± 1.1
	Dexmedetomidine			
	20 μg/kg	39.7 ± 1.1	38.7 ± 1.2	37.3 ± 0.8
	80 μg/kg	34.2 ± 1.8	34.3 ± 1.4	36.3 ± 0.7
	320 μg/kg	36.2 ± 2.4	35.3 ± 0.8	37.5 ± 1.6
Pao_2 (mm Hg)	Saline solution	198 ± 24	215 ± 25	221 ± 14
	Dexmedetomidine			
	20 μg/kg	178 ± 13	175 ± 12	257 ± 47
	80 μg/kg	199 ± 22	204 ± 20	215 ± 13
	320 μg/kg	223 ± 36	218 ± 43	217 ± 41
Base deficit/excess (mEq/L)	Saline solution	−2.7 ± 0.8	−3.0 ± 0.5	−4.6 ± 0.7
	Dexmedetomidine			
	20 μg/kg	−1.1 ± 0.7	−2.9 ± 0.7	−2.5 ± 0.8
	80 μg/kg	0.2 ± 1.1	−0.9 ± 1.6	−1.1 ± 0.8
	320 μg/kg	1.0 ± 2.8	−0.3 ± 2.0	−2.3 ± 1.6

t, Time after start of infusion; $Paco_2$, partial pressure of CO_2 in arterial blood; Pao_2, partial pressure of O_2 in arterial blood; pHa, pH of arterial blood. Results are mean values ± SEM.

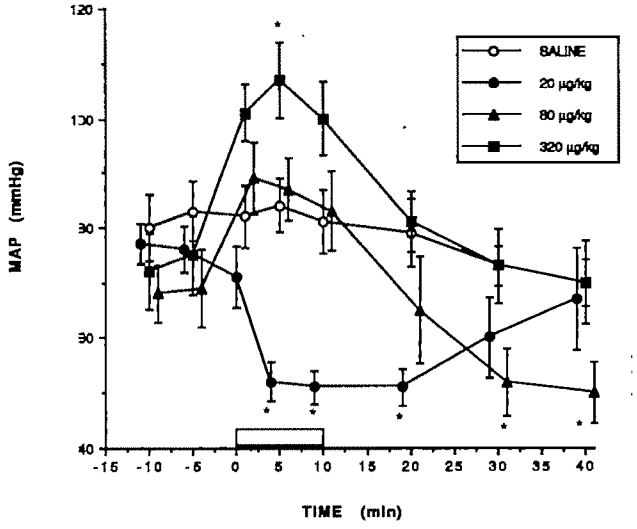


Figure 1. Effect of various doses of dexmedetomidine or saline solution on mean arterial blood pressure (MAP) during phase I of the study. Results are mean ± SEM. *$P < 0.05$ versus saline solution group. *Bar* above the x-axis indicates the duration of drug infusion.

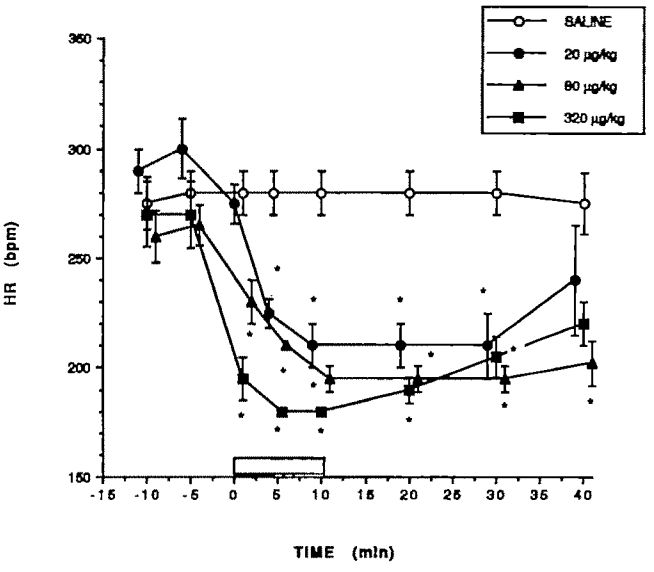


Figure 2. Effect of various doses of dexmedetomidine or saline solution on heart rate (HR) during phase I of the study. Results are mean ± SEM. *$P < 0.05$ versus saline solution group. *Bar* above the x-axis indicates the duration of drug infusion. bpm, beats per minute.

group (Figure 5). A 14% decrease in sagittal sinus blood flow in those animals that received dexmedetomidine did not reach statistical significance ($P = 0.29$) (Figure 6).

Discussion

Dexmedetomidine is a potent agonist of the α_2-subtype of the adrenergic receptor and has been shown to have anesthetic effects in a variety of species, including rats, dogs, rabbits, and humans (12–15). These anesthetic effects are thought to be mediated through postsynaptic α_2-receptors that are widely distributed throughout the brain (13). The dosages of dexmedetomidine (20, 80, and 320 μg/kg) that were used in this study have been

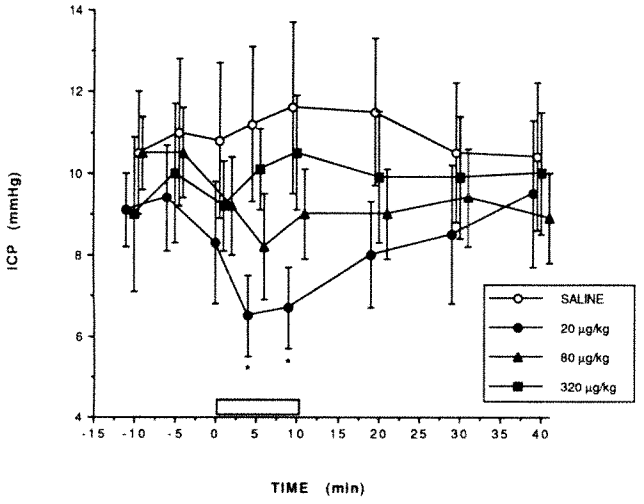


Figure 3. Effect of various doses of dexmedetomidine or saline solution on intracranial pressure (ICP) during phase I of the study. Results are mean ± SEM. $^*P < 0.05$ versus saline solution group. *Bar* above the x-axis indicates the duration of drug infusion.

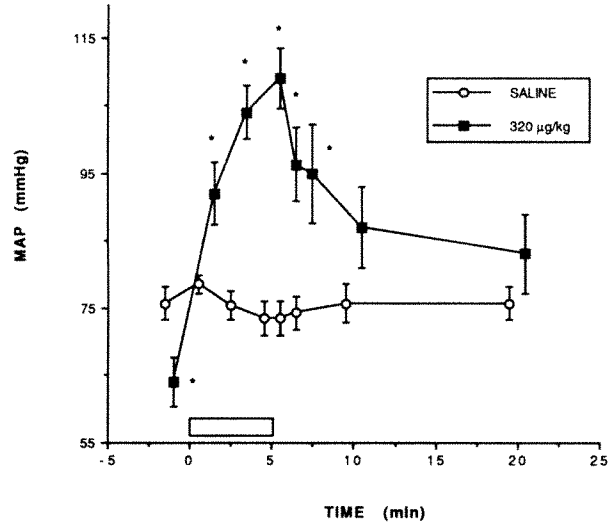


Figure 4. Relative effects of saline solution versus 320 µg/kg of dexmedetomidine on mean arterial blood pressure (MAP) during phase II of the study. Results are mean ± SEM. $^*P < 0.05$ versus saline solution group. *Bar* above the x-axis indicates the duration of drug infusion.

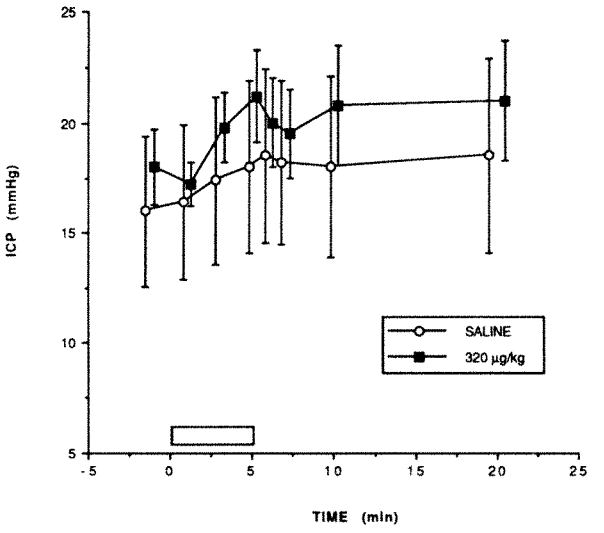


Figure 5. Relative effects of saline solution versus 320 µg/kg of dexmedetomidine on intracranial pressure (ICP) during phase II of the study approximately 1 h after cryogenic lesion. Note elevated baseline for ICP. Results are mean ± SEM. There were no significant differences between the two groups. *Bar* above the x-axis indicates the duration of drug infusion.

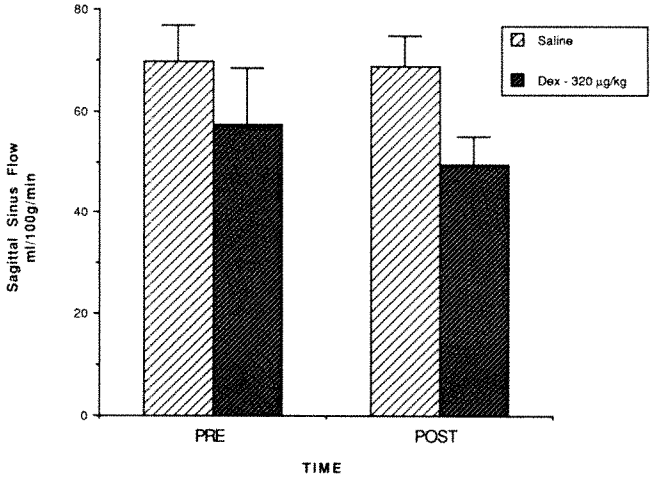


Figure 6. Sagittal sinus blood flow as determined by the hydrogen clearance technique before (PRE) and after (POST) infusion of dexmedetomidine (Dex) (320 µg/kg) or saline solution in animals subjected to cryogenic lesion during phase II of the study.

previously shown (15) to exert mild to profound anesthetic effects in rabbits, as evidenced by a variety of behavioral indices, including loss of righting reflex and failure to withdraw from a painful stimulus. These doses were therefore considered appropriate for investigations of the ICP effects of dexmedetomidine.

In this study, dexmedetomidine produced significant decreases in heart rate. Although bradycardia has been reported in a number of other studies after administration of α_2-agonists (7,8,14–16), the mechanism by which this effect is produced remains unclear. Enhanced baroreceptor sensitivity, increased vagal tone, and decreased release of norepinephrine have all been suggested as contributing factors (17). In the present study, the bradycardia that occurred after the 20-µg/kg dose was associated with a decrease in arterial blood pressure. This would suggest that enhanced baroreceptor sensitivity was not an operative factor.

The effect of dexmedetomidine on arterial blood pressure was dose dependent. At 20 µg/kg, arterial blood pressure decreased by approximately 25 mm Hg

from baseline but had returned to predrug levels at the conclusion of the study 40 min later. Previous studies have reported either hypertension (8,18) or no change in arterial blood pressure (7,14) after dexmedetomidine administration. Thus, the observation of hypotension represents a novel finding. The 80-μg/kg group demonstrated a transient increase in arterial blood pressure immediately after infusion of the drug and then became hypotensive, compared with the saline solution group by t = 30 min. The 320-μg/kg group demonstrated a significant but transient increase in arterial blood pressure (Figure 1).

Recently, it has been speculated that some of the variable arterial blood pressure effects may be due to the type of background anesthetic (19). Specifically, it was conjectured that the use of halothane may prevent a hypertensive response. Analysis of the various studies suggests that the reported variability in arterial blood pressure effects is probably due to differences in the dose and method of administration of dexmedetomidine as well as the intervals at which arterial blood pressure was recorded (20).

In phase I of this study, the ICP effects of various doses of dexmedetomidine were studied in rabbits. The animals had not been subjected to any form of brain injury, and the mean ICP, as measured by a ventricular cannula, was 10.8 ± 3.4 mm Hg. Administration of 20 μg/kg of dexmedetomidine produced a decrease in ICP of approximately 30%, which was noted at 5 and 10 min into the infusion. This decrease was temporally related to a decrease in MAP to approximately 52 mm Hg. Whether the observed decrease in ICP represents an intrinsic cerebral effect or is simply a reflection of a decrease in cerebral perfusion pressure below the lower limit of autoregulation in these halothane-anesthetized animals cannot be determined by this study. The failure of ICP to increase after 320 μg/kg of dexmedetomidine despite a significant increase in arterial blood pressure (from 75 to 107 mm Hg) suggests that this drug either has cerebral vasoconstricting properties in the rabbit or that autoregulation remained intact in these animals despite the 1-MAC concentration of halothane. The latter hypothesis is supported by the fact that administration of phenylephrine in doses sufficient to produce increases in arterial blood pressure similar to those seen with 320 μg/kg of dexmedetomidine also failed to produce any change in ICP.

To investigate further the cerebral effects of dexmedetomidine, the drug was administered after production of a cryogenic brain lesion. Cryogenic lesions have long been used as a model of cerebral injury and are characterized by the breakdown of the blood-brain barrier, vascular congestion, and extravasation of fluid and proteins into the extracellular space (21–24). In the present study, the cryogenic lesion resulted in a mild degree of intracranial hypertension (mean ICP 16.8 mm Hg) and presumably decreased intracranial compliance. In this setting, an anesthetic dose of dexmedetomidine (320 μg/kg) or an equal volume of saline solution was administered. Bradycardia and hypertension similar to that noted in the phase I study were again noted in the animals receiving dexmedetomidine. The ICP gradually increased in both groups after the infusion, but there were no differences at any time between the two groups. Cerebral blood flow was estimated before and immediately after drug administration by use of a sagittal sinus electrode and the hydrogen clearance technique. This methodology has been previously described (25) and is considered to provide a valid estimate of cortical blood flow. Although there were no statistically significant differences in sagittal sinus flow either before or after drug administration, sagittal sinus flow did decrease by 14% in the dexmedetomidine group, whereas there was no change in the saline solution control group.

The α_2-receptors are widely distributed throughout the brain (26) and have been found on the cerebral arterioles where they mediate vasoconstriction in response to stimulation by norepinephrine (27). Previous studies have demonstrated marked reductions in cerebral blood flow without a corresponding decrease in metabolic rate after the administration of dexmedetomidine (7,8). This response is thought to be due to α_2-receptor-induced arteriolar vasoconstriction. Cerebral vasoconstriction may result in corresponding decreases in cerebral blood volume and thus in ICP. This study demonstrates that, in the rabbit, dexmedetomidine either decreases (20 μg/kg) or has no effect (80 and 320 μg/kg) on ICP. The failure of ICP to increase in the 320-μg/kg group despite a 32-mm Hg increase in arterial blood pressure suggests a cerebral vasoconstrictive effect that may be due to a direct action of the drug on the cerebral vessels or to preservation of autoregulation. We conclude that dexmedetomidine, in a wide range of dosages and despite the presence or absence of a cryogenic brain lesion, has minimal effects on ICP in rabbits.

The authors gratefully acknowledge the support and assistance provided by Drs. Mervyn Maze and Antero Kallio.

References

1. Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Kärki NT. Evidence for medetomidine as a selective and potent agonist at α-2-adrenoreceptors. J Auton Pharmacol 1986;5:275–84.
2. Virtanen R, Savola J-M, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an α-2-adrenoceptor agonist. Eur J Pharmacol 1988;150:9–14.

3. Aantaa R, Kallio A, Kanto J, Scheinin H, Scheinin M. Dexmedetomidine reduces thiopental anesthetic requirements in man (abstract). Anesthesiology 1989;71:A253.
4. Aho M, Lehtinen A-M, Laatikainen T, Korttila K. Effects of intramuscular clonidine on hemodynamic and plasma β-endorphin responses to gynecologic laparoscopy. Anesthesiology 1990;72:797–802.
5. Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Anesthesiology 1991;75:328–32.
6. Doze VA, Chen B-X, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central α-2 adrenoceptors. Anesthesiology 1989;71:75–9.
7. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent α-2 agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990;71:125–9.
8. Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an α-2 adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 1990;70:624–30.
9. Halsey JH, Capra NF, McFarland RS. Use of hydrogen for measurement of regional cerebral blood flow: problem of intercompartmental diffusion. Stroke 1977;8:351–7.
10. Pasztor E, Symon L, Dorsch NWC, Branston NM. The hydrogen clearance method in assessment of blood flow in cortex, white matter and deep nuclei of baboons. Stroke 1973;4:556–67.
11. Pearce RA, Adams JM. Measurement of rCBF by H_2 clearance: theoretical analysis of diffusion effects. Stroke 1982;13:347–55.
12. Aho M, Lehtinen A-M, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology 1991;74:997–1002.
13. Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic α-2 adrenergic receptor. Anesthesiology 1988;69:818–23.
14. Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α-2 adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 1988;67:611–5.
15. Zornow MH. Ventilatory, hemodynamic and sedative effects of the α-2 adrenergic agonist, dexmedetomidine. Neuropharmacology 1991;30:1065–71.
16. Scheinin M, Kallio A, Koulu M, Viikari J, Scheinin H. Sedative and cardiovascular effects of medetomidine, a novel selective α-2-adrenoceptor agonist, in healthy volunteers. Br J Clin Pharmacol 1987;24:443–51.
17. Maze M, Tranquilli W. α-2 Adrenoceptor agonists: defining the role in clinical anesthesia. Anesthesiology 1991;74:581–605.
18. Bloor BC, Alper G, Frankland M, Flacke JW. Nifedipine attenuates the acute hemodynamic changes that occur with intravenous dexmedetomidine in dogs. Anesth Analg 1989;68: S32.
19. Scheller MS, Zornow MH. Are the hemodynamic effects of dexmedetomidine influenced by the background anesthetic? (Letter). Anesth Analg 1991;72:408.
20. Karlsson BR, Steen PA. Are the hemodynamic effects of dexmedetomidine influenced by the background anesthetic in response (Letter). Anesth Analg 1991;72:408–9.
21. Clasen RA, Bezkorovainy A, Pandolfi S. Protein and electrolyte changes in experimental cerebral edema. J Neuropathol Exp Neurol 1982;41:113–28.
22. Gazendam J, Go KG, van Zanten AK. Composition of isolated edema fluid in cold-induced brain edema. J Neurosurg 1979; 51:70–7.
23. Herrmann HD, Neuenfeldt D. Development and regression of a disturbance of the blood-brain barrier and of edema in tissue surrounding a circumscribed cold lesion. Exp Neurol 1972;34: 115–20.
24. Orita T, Nishizaki T, Kamiryo T, Harada K, Aoki H. Cerebral microvascular architecture following experimental cold injury. J Neurosurg 1988;68:608–12.
25. Scremin OU, Sonnenschein RR, Rubinstein EH. Cerebrovascular anatomy and blood flow measurements in the rabbit. J Cereb Blood Flow Metab 1982;2:55–66.
26. Unnerstall JR, Kopajtic TA, Kuhar MJ. Distribution of α-2 agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res 1984;7:69–101.
27. Busija DW, Leffler CW. Exogenous norepinephrine constricts cerebral arterioles via α-2 adrenoceptors in newborn pigs. J Cereb Blood Flow Metab 1987;7:184–8.

Methylprednisolone Does Not Decrease Eicosanoid Concentrations or Edema in Brain Tissue or Improve Neurologic Outcome After Head Trauma in Rats

Yoram Shapira, MD, PhD, Alan A. Artru, MD, Gal Yadid, PhD, and Ester Shohami, PhD

Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington, and Department of Pharmacology, The Hebrew University Haddassah Medical School, Jerusalem, Israel

Methylprednisolone was recently reported to significantly improve motor and sensory function after acute spinal cord injury in patients. Our study was designed to determine whether methylprednisolone exerts a beneficial effect after head injury. Diethyl ether-anesthetized rats were assigned to receive surgery with no cranial impact and no methylprednisolone (group A, $n = 13$); surgery with no cranial impact and intraperitoneal methylprednisolone (≥60 mg/kg) (group B, $n = 8$); surgery with cranial impact and no methylprednisolone (group C, $n = 8$, and group E, $n = 8$); or surgery with cranial impact and methylprednisolone (≥60 mg/kg) (group D, $n = 15$, and group F, $n = 13$). Neurologic severity score was determined at 1, 2, 4, and 24 h (when appropriate) after injury, and brain tissue eicosanoid levels and cerebral edema were determined when the animals were killed (4 h after injury in groups C and D and 24 h after injury in groups E and F). Treatment with methylprednisolone did not improve neurologic severity score or edema formation and did not alter brain tissue levels of prostaglandin E_2, thromboxane B_2, or 6-keto-prostaglandin $F_{1\alpha}$ at any time period. The authors conclude that methylprednisolone does not exert a beneficial effect on brain tissue edema or functional activity after cranial impact in rats.

(Anesth Analg 1992;75:238–44)

We previously characterized the changes in brain tissue prostaglandin and thromboxane levels, brain edema, and neurologic function in a rat model of nonpenetrating, blunt cranial impact (1–3). We reported that increased rates of prostaglandin and thromboxane synthesis and release from brain slices were demonstrated as early as 15 min after injury, were maximal at 1–24 h, and gradually resolved by 10 days after injury (3). Brain edema was demonstrable as early as 15 min after injury, was maximal at 18–48 h, and gradually resolved by 10 days after injury (1). Neurologic function was maximally impaired immediately after injury and gradually resolved to almost no residual deficit by 10 days after injury (1,2).

In subsequent studies, we examined the effects of treatment with dexamethasone sodium phosphate and indomethacin before and after injury and treatment with free dexamethasone after injury in the same model (4). We reported that prostaglandin synthesis was significantly decreased by indomethacin or free dexamethasone but not dexamethasone sodium phosphate, both in sham- and head-injured rats. In contrast, none of the treatments significantly changed brain edema or neurologic outcome.

Recently, Bracken et al. (5), in a multicenter, randomized, double-blind placebo-controlled trial, reported that methylprednisolone (30 mg/kg IV) as a bolus dose followed by 5.4 mg/kg for the next 23 h improved neurologic outcome in patients with acute spinal injury. We hypothesized that methylprednisolone might also decrease brain eicosanoid and edema formation and improve neurologic outcome after head trauma. Our hypothesis is consistent with two previous reports that methylprednisolone improved neurologic outcome after head trauma in mice (6) and humans (7); however, in both studies, the results may have been affected by the methodology. In the study in mice, brain edema and eicosanoid levels were not examined, and neurologic outcome was examined only at 1 h after head injury (6). Because evolution of neurologic injury after head trauma is known to occur over many hours, it is not certain whether the beneficial effect at 1 h was a transient finding or indicative of the potential for

Accepted for publication March 31, 1992.

Address correspondence to Dr. Shapira, Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, WA 98195.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

long-lasting neurologic improvement. In the second study, the positive results in a subset of patients may have occurred because baseline Glasgow coma scores were higher in the high-dose methylprednisolone group than in the combined low-dose/placebo group (7).

Accordingly, the present study was designed to examine for 24 h the effect of methylprednisolone on brain eicosanoid concentrations and edema formation and neurologic status after closed-head trauma or sham surgery in rats. The methylprednisolone dose regimen was designed according to the previously reported study of Braughler et al. (8).

Methods

The rats in this study were cared for according to the Guiding Principles in the Care and Use of Animals, as approved by the Council of the American Physiologic Society and published in their *Guide for Authors*. The protocol for this model was reviewed and approved by the Animal Care Committee of the University of Washington. Seventy-four male Sabra rats, weighing 330 ± 42 g (mean value ± SD) were anesthetized in a bell jar containing ether-drenched cotton. Rats breathed spontaneously, and their tracheas were not intubated. Corneal reflexes were assessed at intervals, and anesthesia was considered sufficient for surgery once corneal reflexes were abolished. Maintenance of adequate anesthesia for the experimental procedure was confirmed by repeated assessment of corneal and pupillary reflexes. Rats were randomly assigned to one of six experimental groups. The number of rats allocated to the experimental groups was calculated to permit statistical analysis with a significance level of 0.05 and power of 0.80 for the normally distributed data (i.e., brain tissue specific gravity, water content, and eicosanoid levels), as recommended for biological data (9). For the hypothesis that methylprednisolone increased specific gravity and decreased water content and eicosanoid levels, compared with no treatment after closed-head trauma, the equation for sample size determination was as follows:

$$n = \frac{\sigma^2(z_{1-\beta} + z_{1-\alpha})^2}{(\mu_0 - \mu_1)^2},$$

where n is the number of rats, σ the standard deviation, $1 - \beta$ power, α the level of significance, and $\mu_0 - \mu_1$ the difference between mean values considered clinically significant. The σ values taken from previous studies (0.0011 for specific gravity [2], 0.4% for water content [10], and 50 pg/mg protein for eicosanoid levels [3], respectively) and the $\mu_0 - \mu_1$ values based on previous studies (0.001 for specific gravity [2], 0.5% for water content [10], and 60 pg/mg protein for eicosanoid levels [3], respectively) yielded a minimal sample size of eight (the largest of the three calculated n values). Accordingly, the minimal number of rats assigned to groups where no cranial impact was delivered (groups A and B) was eight. In this model, 10%–30% of rats receiving closed cranial impact were expected to die of apnea immediately after injury (1–4). Accordingly, the minimal number of rats assigned to groups where cranial impact was delivered (groups C–F) was 11.

In group A (n = 13), the scalp was incised longitudinally and separated to expose the underlying skull. No cranial impact was delivered, and no methylprednisolone was given. The scalp incision was closed; anesthesia was discontinued; and rats were returned to their cages, where they were allowed free access to food pellets and water. Rats were killed at 24 h. In group B (n = 8), the skull was exposed surgically; no cranial impact was delivered; and methylprednisolone was administered intraperitoneally (IP) in divided doses. The dosing schedule for methylprednisolone was as follows: 30 mg/kg IP was administered immediately after exposing the skull, 15 mg/kg IP at 2 h after the scalp incision was closed, and 15 mg/kg IP at 4 h after discontinuation of anesthesia and return of rats to their cages and every 4 h thereafter until the rats were killed. In groups C–F (n = 11,16,11,15), the skull was exposed, and a cranial impact was delivered at a prefixed point over the left hemisphere, 1–2 mm lateral from the midline on the skull convexity by a special weight-drop device (1). The weight-drop device was designed to deliver a standard blow to the cranium, resulting in a controlled head injury. Impact is delivered by a silicone-coated metal tip that extrudes from a platform falling down a frame. Settings on the frame control the distance of the fall off the platform (1). The reproducibility of the impact was previously determined by measuring the velocity developed during the free fall of the platform and the change in the velocity of the tip on collision with the target (1). After head trauma, animals spontaneously breathing were randomized into groups C–F.

Nine of the rats originally designated for groups C–F died of apnea immediately after the impact and were excluded from the study. All animals that survived a period of 5 min after impact breathed spontaneously and lived until they were killed at 4 or 24 h. In groups C (n = 8) and E (n = 8), no methylprednisolone was administered. Rats in group C were killed at 4 h and rats in group E at 24 h. In groups D (n = 15) and F (n = 13), methylprednisolone was administered intraperitoneally according to the same dosing schedule as group B. Rats in group D were killed at 4 h and rats in group F at 24 h.

At the time of killing, rats were decapitated and their brain immediately removed (42 ± 6 s). Coronal sections 1.5 mm in width were made with a brain tissue slicer (D. Jacobowitz, National Institutes of Health, Bethesda, Md.). Tissue samples of gray matter, 20–50 mg each, were cut on a frozen plate from areas just adjacent to the zone of maximal macroscopic damage in the left hemisphere and the corresponding contralateral areas of the right hemisphere. In each case, specific gravity, water content, and eicosanoid levels were determined.

Systemic Values

An additional group of 10 rats was prepared for determination of blood pressure at several time points in the course of the experiment. Rats were anesthetized with ether, and a polyethylene catheter (PE-50; Clay Adams, N.J.) was inserted into the femoral artery. Mean arterial blood pressure was determined by electronic integration of systolic and diastolic pressures and recorded by a pressure transducer on a polygraph recorder. Arterial blood pressure recordings were performed before and immediately after head trauma and at 5, 10, 15, 30, and 60 min and 8 and 18 h after injury.

A second additional group of six rats was prepared for determination of arterial blood gas tensions and blood glucose and electrolyte levels before head trauma and 30 and 90 min after injury. Rats were anesthetized with ether, and a catheter was inserted into the femoral artery. Blood pH, arterial O_2 tension (Pao_2), arterial CO_2 tension ($Paco_2$), HCO_3, glucose, sodium, potassium, chloride, and calcium levels were determined from 0.5-mL samples with a NOVA Stat Profile Five (Nova Biomedical, Waltham, Mass.).

Neurologic Severity Score

The neurologic status of the rats was evaluated at 1, 2, 4, and 24 h (where appropriate) after skull exposure with or without cranial impact. This evaluation was done with a neurologic severity score (NSS) that was developed (2) to define the clinical condition of rats after head trauma. The criteria for scoring are summarized in Table 1. The score consists of a maximal score of 24 points at 1 h after trauma and a maximal score of 20 points at 2, 4, and 24 h after trauma. The examination was carried out under quiet conditions in a lighted room by an observer who was unaware of the experimental treatment. With the NSS used in this study, a maximal score represents the most severe disturbance of neurologic function, and a lower score represents less functional impairment (1).

Table 1. Neurologic Severity Score for Rats After Head Trauma

	Points	
	At 1 h after head trauma	At 2, 4, and 24 h after trauma
Inability to exit from a circle (50 cm in diameter) when left in the center		
For 30 min	1	—
For 60 min	1	—
For >60 min	1	1
Loss of righting reflex		
For 20 min	1	—
For 40 min	1	—
For >40 min	1	1
Hemiplegia (inability of rat to resist forced changes in position)	1	1
Flexion of hindlimb when raised by the tail	1	1
Inability to walk straight when placed on the floor	1	1
Reflexes		
Pinna reflex	1	1
Corneal reflex	1	1
Startle reflex	1	1
Clinical grade		
Loss of seeking behavior	1	1
Prostration	1	1
Limb reflexes: loss of placing reflexes		
Forelimbs		
Left	1	1
Right	1	1
Hindlimbs		
Left	1	1
Right	1	1
Functional test		
Failure in beam-balancing task (1.5 cm wide)		
For 20 s	1	1
For 40 s	1	1
For >40 s	1	1
Failure in beam-walking task		
8.5 cm wide	1	1
5 cm wide	1	1
2.5 cm wide	1	1
Maximal points	24	20

Specific Gravity Measurements

The specific gravity of brain tissue was determined according to the method described previously by Marmarou et al. (11). In brief, the tissue segments were placed on top of linear gradient columns of kerosene and bromobenzene, which were calibrated with K_2SO_4. Specific gravity of the tissue was calculated from the standard curve by measuring its equilibrium position in the column.

Water Content

Each tissue sample was placed on a piece of aluminum foil and weighed for tissue wet weight (WW). It was then dried in a dessicating oven at 105°C for 24 h and reweighed to obtain dry weight (DW). Tissue water concentration was calculated as (WW − DW)100/WW.

Eicosanoid Extraction and Determination

Immediately after decapitation and removal of the brain, tissue samples (approximately 20 mg each) were frozen on dry ice and stored at −80°C. Tissue samples from each animal were taken from both the injured (parietal) and frontal cortex from the contused hemisphere and from the corresponding sites on the contralateral hemisphere. The slices were sonically disrupted in 600 μL of buffer (Tris-HCl 0.05 M, NaCl 0.1 M, and ethylenediaminetetraacetate [EDTA] 0.2 mM, 9:1, pH 7.0). Aliquots were taken from the homogenate for protein determination by the method of Lowry et al. (12), and the homogenate was then centrifuged at 4000 rpm for 15 min at 4°C. The supernatant fluid was decanted, and 100 μL were taken for each of the following radioimmunoassays: prostaglandin E_2 (PGE_2), thromboxane B_2 (TXB_2) (the stable metabolite of thromboxane A_2), and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) (the stable metabolite of prostacyclin). The assay was carried out as described previously by Shohami et al. (13) using ^{3}H-labeled prostaglandins (100–200 Ci/mM) (New England Nuclear, North Bellerica, Mass.), specific antibodies (<0.1% cross-reactivity with other prostaglandins) (purchased from Professor L. Levine, Brandeis University, Waltham, Mass.), and standard prostaglandins (Sigma, St. Louis, Mo.).

Statistical Analysis

The data are presented as mean values ± SD. Brain tissue specific gravity, water content, and eicosanoid values were analyzed by analysis of variance, followed by posthoc testing with Student-Newman-Keul's test. The NSS was analyzed with the Mann-Whitney test for nonparametric data. A P value of <0.05 was considered significant.

Results

Systemic Values

Mean arterial blood pressure was 98 ± 10 mm Hg before head trauma and increased immediately after injury. The maximal increase occurred at 10 min after injury (118 ± 10 mm Hg), and thereafter pressure gradually returned to values before injury. By 8 h after injury, mean arterial blood pressure was not significantly different from values before injury. Arterial blood gas tensions and glucose and electrolyte concentrations are presented in Table 2. Values at 30 and 90 min after injury were not significantly different from values before injury.

Table 2. Arterial Blood Gas Tensions and Blood Glucose and Electrolyte Concentrations (mean values ± SD) (n = 6)

	Before injury	30 min after injury	60 min after injury
pH	7.37 ± 0.05	7.31 ± 0.05	7.35 ± 0.05
Pao_2 (mm Hg)	412 ± 33	420 ± 33	394 ± 37
$Paco_2$ (mm Hg)	41.4 ± 4.4	39.3 ± 1.0	43.7 ± 5.1
Bicarbonate (mEq/L)	25.2 ± 1.6	21.7 ± 2.0	22.2 ± 0.8
Glucose (mg/dL)	188 ± 21	219 ± 22	211 ± 37
Sodium (mEq/L)	143 ± 2	131 ± 4	132 ± 5
Potassium (mEq/L)	5.2 ± 0.7	5.5 ± 1.0	6.1 ± 0.6
Chloride (mEq/L)	109 ± 3	103 ± 6	103 ± 5
Calcium (mEq/L)	2.2 ± 0.1	1.9 ± 0.1	2.0 ± 0.1

Neurologic Status

The NSS of all rats where cranial impact was delivered (groups C–F) is shown for 1, 2, 4, and 24 h after impact in Figure 1. Between-group comparisons indicated that at each time period, the NSS of rats where cranial impact was delivered and methylprednisolone was administered (groups D and F) was not significantly different from the NSS of rats where cranial impact was delivered but no methylprednisolone was administered (groups C and E). Within-group comparisons indicated that NSS at 24 h after cranial impact was significantly decreased compared to NSS at 1 h after cranial impact, indicating partial neurologic recovery whether or not methylprednisolone was administered.

Edema Formation

The specific gravity and water content of cortical slices that were taken from the injured and from the corresponding contralateral hemisphere in both the treated and untreated rats are presented in Figures 2 and 3. Between-group comparisons indicated that specific gravity and water content of the injured hemisphere from rats where cranial impact was delivered and methylprednisolone was administered (groups D and F) were not significantly different from specific gravity and water content of the injured hemisphere from rats where cranial impact was delivered and no methylprednisolone was administered (groups C and E). Similarly, specific gravity and

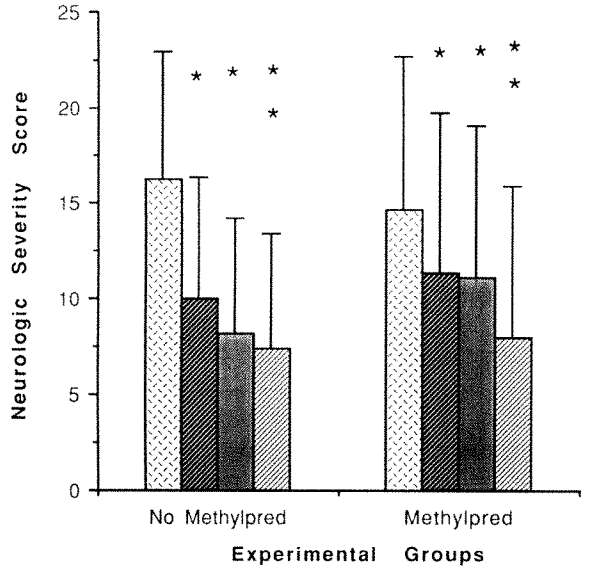


Figure 1. Neurologic severity scores (NSS, reading from left to right) at 1, 2, 4, and 24 h after cranial impact are shown. *Left*, data from rats not receiving methylprednisolone (methylpred); *right*, data from rats receiving methylprednisolone. Higher scores indicate more severe neurologic deficit. Results are mean values ± SD. There was no statistically significant difference between the treated and untreated animals. In both groups there was a statistically significant improvement over time. $^*P < 0.01$; $^{\dagger}P < 0.001$.

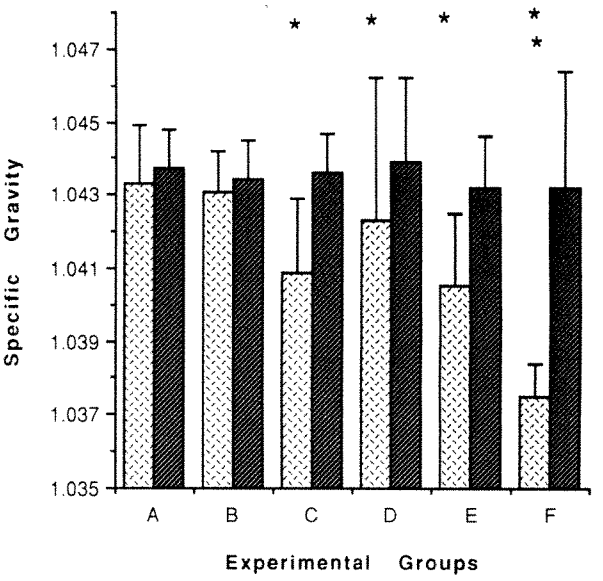


Figure 2. *Columns* represent specific gravity of the contused and uncontused hemispheres of rats with no cranial impact and no methylprednisolone (group A), methylprednisolone and no cranial impact (group B), cranial impact and no methylprednisolone (groups C and E, 4 and 24 h after injury, respectively), and methylprednisolone followed by cranial impact (groups D and F, 4 and 24 h after injury, respectively). Results are mean values ± SD. There was no statistically significant difference between the treated and untreated animals. Specific gravity of contused (*left*) hemispheres was decreased compared with that in rats with no cranial impact and the untraumatized (*right*) hemisphere. $^*P < 0.05$; $^{\dagger}P < 0.01$.

water content of the noninjured hemisphere from traumatized and treated rats (groups D and F) were not significantly different from specific gravity and water content of the noninjured hemisphere from either traumatized and untreated rats (groups C and E) or nontraumatized rats (groups A and B).

Brain tissue specific gravity and water content in rats receiving methylprednisolone and no cranial impact (group B) were not significantly different from that in rats receiving no methylprednisolone and no cranial impact (group A). Within-group comparisons indicated that specific gravity was decreased and water content was increased ($P < 0.01$) in the injured hemisphere compared with specific gravity and water content both in the noninjured (right) hemisphere in groups C–F and in the rats receiving no cranial impact (groups A and B).

Eicosanoid Extraction and Determination

Baseline (group A) values from left parietal areas were PGE_2 of 251 ± 40, TXB_2 of 342 ± 63, and 6-keto-$PGF_{1\alpha}$ of 155 ± 28 pg/mg protein. Between-group comparisons indicated that PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ from the injured (left) parietal area from rats where cranial impact was delivered and methylprednisolone was administered (mean values for groups D and F: 767 ± 168, 457 ± 92, and 281 ± 67 pg/mg protein, respectively) were not significantly different from PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ from the injured parietal area from rats where cranial impact was delivered and methylprednisolone was not administered (groups C and E). Similarly PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ from the noninjured parietal areas and both frontal regions in groups D and F were not different from those in groups C and E. In addition, brain tissue eicosanoid levels in rats receiving methylprednisolone and no cranial impact (group B) were not significantly different from those in rats receiving no methylprednisolone and no cranial impact (group A). Within-group comparisons indicated that brain tissue eicosanoid levels were increased in the injured (left) hemisphere compared with levels in the noninjured (right) hemisphere at 24 h after injury (groups E and F).

Discussion

The first principal finding of this study was that the NSS at 4 and 24 h after head injury was not improved by methylprednisolone. This finding is consistent with the negative results reported with other glucocorticoids during head trauma (4,14–16), global isch-

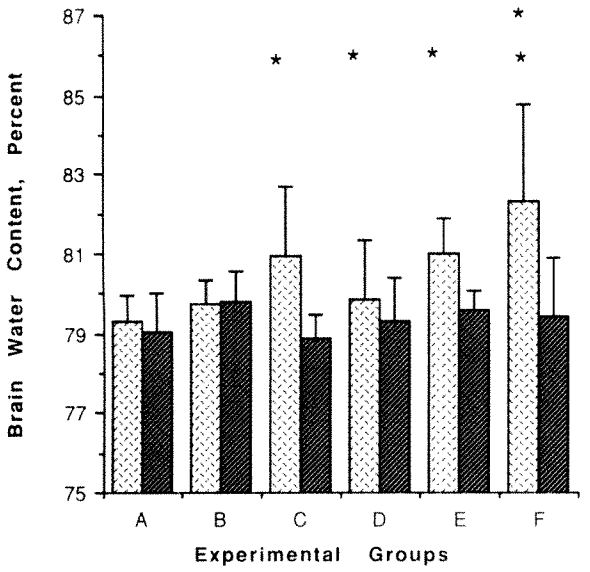


Figure 3. *Columns* represent percentage of water content of the contused and uncontused hemispheres of rats with no cranial impact and no methylprednisolone (group A), methylprednisolone and no cranial impact (group B), cranial impact and no methylprednisolone (groups C and E, 4 and 24 h after injury, respectively), and methylprednisolone followed by cranial impact (groups D and F, 4 and 24 h after injury, respectively). Results are mean values ± SD. There was no statistically significant difference between the treated and untreated animals. Brain water content of contused (*left*) hemispheres was increased compared with that in rats with no cranial impact and the untraumatized (*right*) hemisphere. $^*P < 0.05$; $^{**}P < 0.01$.

emia (17), and spinal cord injury (18). In contrast, methylprednisolone was reported to improve neurologic outcome after spinal cord injury (5,8,19), ischemia (20), and head trauma (6,7). However, as noted earlier, the positive results after head trauma in mice may relate to the short period of neurologic evaluation (6), whereas the positive results in a subset of patients may have occurred because baseline Glasgow coma scores were higher in the high-dose methylprednisolone group (7).

The second principal finding of this study was that brain tissue water content and specific gravity in injured tissue at 4 and 24 h after cranial impact were not improved by methylprednisolone. This finding is consistent with studies of other glucocorticoids in head trauma (4,21). In contrast, Bremer et al. (20) reported that methylprednisolone improved brain edema 24 h after focal ischemia in primates. There are no previous reports of studies that evaluated brain edema after methylprednisolone treatment in head trauma.

The third principal finding of this study was that methylprednisolone did not minimize formation of PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ in injured brain. This finding is consistent with the negative results reported for several other glucocorticoids in head trauma (4,21). In contrast, free dexamethasone was found to decrease prostaglandin levels after head trauma (4). Although free dexamethasone decreased prostaglandin levels, this effect was not associated with decreased edema formation or improved neurologic outcome. Although in the present study methylprednisolone did not increase brain tissue specific gravity or decrease NSS, brain tissue water content, or formation of PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ after injury, it is possible that another dose regimen may have yielded different results.

The present study and most previous ones report no decrease of brain edema or eicosanoid levels with glucocorticoids. Thus, in the studies reporting improved neurologic outcome with glucocorticoids, it seems likely that effects other than those on brain edema or eicosanoid levels contribute to the favorable outcome. The most frequently given explanation for improved neurologic outcome with glucocorticoids is membrane stabilization manifested by maintenance of the capillary endothelial membranes (22) and preservation of lysosomal integrity (23) and membrane-bound enzymes (24). Chan et al. (25) and Gamache and Ellis (26) reported that glucocorticoids act mainly to decrease the permeability of the blood-brain barrier and do not act on brain edema itself. Demopoulous et al. (27) reported that glucocorticoids stabilize membranes and do not inhibit prostaglandin synthesis. Hall (6) suggested that the steroids act on the integrity of the cell membranes, inhibit free radicals and oxygenation of lipids, and do not inhibit prostaglandin synthesis.

In studies reporting no improvement of neurologic outcome with glucocorticoids after head trauma, failure of glucocorticoids to improve outcome may relate to previous reports that glucocorticoids exert adverse effects on compromised neural tissue. McEwen et al. (28,29) showed that glucocorticoid administration during stress may injure neurons in the hippocampus. It was speculated that glucocorticoids impair the energy metabolism of these neurons (30). Others reported that steroids may hasten the death of hippocampal neurons (31–33). Sapolsky et al. (34) demonstrated in tissue cultures that the addition of glucocorticoid decreased their viability after neurotoxin administration compared with controls. A concentration of 10^{-9} M corticosterone, which is in the range of normal physiologic levels, increased the damage. The addition of glucose to the cultures that contained both the toxin and glucocorticoid increased cell viability. Glucose added to cultures containing toxin only did not change the initial viability. Excision of the adrenal gland after hypoxia or ischemia decreased the damage observed in the hippocampus (35,36).

In summary, methylprednisolone did not improve NSS, brain water content, or specific gravity or min-

imize brain tissue eicosanoid formation after nonpenetrating cranial impact in rats. These findings are consistent with previous reports wherein glucocorticoids failed to improve neurologic outcome, neural tissue edema, or neural tissue eicosanoid levels in other forms of neural tissue injury. Our results did not confirm our hypothesis that methylprednisolone would decrease brain edema and eicosanoid levels and improve neurologic outcome after head trauma. These findings do not support the use of methylprednisolone for treatment of head-injured patients.

References

1. Shapira Y, Shohami E, Sidi A, Soffer D, Freeman S, Cotev S. Experimental closed head injury in rats: mechanical, pathophysiological, and neurological properties. Crit Care Med 1988;16:258–65.
2. Shapira Y, Yadid G, Cotev S, Niska A, Shohami E. Protective effect of MK-801 in experimental brain injury. J Neurotrauma 1990;3:131–9.
3. Shohami E, Shapira Y, Sidi A, Cotev S. Head injury induces increased prostaglandin synthesis in rat brain. J Cereb Blood Flow Metab 1987;7:58–63.
4. Shapira Y, Davidson E, Weidenfeld Y, Cotev S, Shohami E. Dexamethasone and indomethacin do not affect brain edema following head injury in rats. J Cereb Blood Flow Metab 1988;8:395–402.
5. Bracken MB, Shepard MJ, Collins WF, et al. A randomized controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. N Engl J Med 1990;322: 1405–11.
6. Hall ED. High dose glucocorticoid treatment improves neurological recovery in head injured mice. J Neurosurg 1985;62: 882–7.
7. Giannotta SL, Weiss MH, Apozzo MLJ, Martine E. High dose glucocorticoids in the management of severe head injury. Neurosurgery 1984;15:497–501.
8. Braughler JD, Hall ED, Means ED, Waters TR, Anderson DK. Evaluation of an intensive methylprednisolone sodium succinate dosing regimen in experimental spinal cord injury. J Neurosurg 1987;67:102–5.
9. Rosner B. Hypothesis testing: one-sample inference. In: Rosner B, ed. Fundamentals of biostatistics. Boston: Duxbury Press, 1982:171–224.
10. Naruse S, Aoki Y, Takei R, Horikawa Y, Ueda S. Effects of atrial natriuretic peptide on ischemic brain edema in rats evaluated by proton magnetic resonance method. Stroke 1991; 22:61–5.
11. Marmarou A, Tanaka K, Shulman K. An improved gravimetric measure of cerebral edema. J Neurosurg 1982;56:246–53.
12. Lowry OH, Rosebrough NH, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265–75.
13. Shohami E, Rosenthal J, Lavy S. The effect of incomplete cerebral ischemia on prostaglandin levels in rat brain. Stroke 1982;13:494–9.
14. Braakman R, Schouten HJA, Dischoeck MB, Minderhound JM. Megadose steroids in severe head injury. Results of a prospective double blind clinical trial. J Neurosurg 1983;58:326–30.
15. Gudeman SK, Miller JD, Becker DP. Failure of high dose steroid therapy to influence intracranial pressure in patients with severe head injury. J Neurosurg 1979;51:301–6.
16. Saul TG, Ducker TB, Salcman M, Carro E. Steroids in severe head injury. J Neurosurg 1981;54:596–600.
17. Jastremski M, Sutton-Tyrrell K, Vaagenes P, Abramson N, Heiselman D, Safar P. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. JAMA 1989;262:3427–30.
18. Faden AI, Jacobs TP, Patrick DH, Smith MT. Megadose corticosteroid therapy following experimental traumatic spinal injury. J Neurosurg 1984;60:712–7.
19. Braughler JM, Hall ED. Effect of multidose methylprednisolone sodium succinate administration on injured cats spinal cord neurofilament degeneration and energy metabolism. J Neurosurg 1984;61:290–5.
20. Bremer AM, Yamady K, West CR. Ischemic cerebral edema in primates: effects of acetazolamide phenytoin, barbital, dexamethasone and methylprednisolone on brain water and electrolytes. Neurosurgery 1980;6:149–54.
21. Tornheim PA, McLaurin RL. Effect of dexamethasone on cerebral edema from cranial impact in the cat. J Neurosurg 1978;48:220–7.
22. Richardson HD, Nakamaura S. An EM study of spinal cord edema and the effect of treatment with steroids, manitol, and hypothermia. Proc Veterans Adm Spinal Cord Inj Conf 1971; 18:10–6.
23. Eidelberg E. Cardiovascular response to experimental spinal cord compression. J Neurosurg 1973;38:326–31.
24. Weissman G, Dingle JT. Release of lysosomal proteases by ultraviolet irradiation and inhibition by hydrocortisone. Exp Cell Res 1961;25:207–10.
25. Chan PH, Schmidley JW, Fishman RA, Longar SM. Brain injury, edema and vascular permeability changes oxidized by oxygen-derived free radicals. Neurology 1984;34:315–20.
26. Gamache DA, Ellis EF. Effect of dexamethasone, indomethacin, ibuprofen, and probenecid on carrageenan-induced brain inflammation. J Neurosurg 1986;65:686–92.
27. Demopoulous HB, Milvy P, Kakari S, Ranaohoff J. Molecular aspects of membrane structure in cerebral edema. In: Reulen HJ, Schurmann K, eds. Steroids and brain edema. Berlin: Springer-Verlag, 1972:29–39.
28. McEwen BS, DeKolt ER, Rostene W. Adrenal steroids receptors and actions in the nervous system. Physiol Rev 1986;66: 1121–88.
29. McEwen BS, Weiss JM, Schwartz LS. Selective retention of corticosterone by limbic structures in rat brain. Nature 1968; 220:911–2.
30. Sapolsky RM. Glucocorticoid toxicity in the hippocampus: reversal by supplementation with brain fuels. J Neurosci 1986;6:2240–4.
31. Landfield PW, Baskin RK, Pitler TA. Brain aging correlates: retardation by hormonal-pharmacological treatments. Science 1981;214:581–4.
32. Sapolsky RM, Krey L, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev 1986;7:284–9.
33. Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. Science 1985; 229:1397–400.
34. Sapolsky RM, Packan DR, Vale WW. Glucocorticoid toxicity in the hippocampus: in vitro demonstration. Brain Res 1988;453: 367–71.
35. Sapolsky RM. Glucocorticoid toxicity in the hippocampus: temporal aspects synergy with a kainic acid. Neuroendocrinology 1986;43:440–4.
36. Sapolsky RM, Krey L, McEwen BS. Prolonged glucocorticoid exposure reduced hippocampal neurons number: implication for aging. J Neurosci 1985;5:1221–6.

Epidural Patient-Controlled Analgesia: An Alternative to Intravenous Patient-Controlled Analgesia for Pain Relief After Cesarean Delivery

Robert K. Parker, DO, and Paul F. White, PhD, MD, FFARACS

Division of Clinical Research, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri, and Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas

Epidural administration of an opioid analgesic by means of a patient-controlled analgesia (PCA) system was compared with conventional intravenous PCA for pain relief after cesarean delivery. One hundred seventeen healthy women were randomly assigned to receive hydromorphone either intravenously (IV-PCA) or epidurally (EPI-PCA) after cesarean delivery with epidural bupivacaine for operative anesthesia. The hydromorphone requirements were 3.4 and 4.2 times more in the IV-PCA group on the first ($P < 0.01$) and second ($P < 0.01$) postoperative days, respectively. The mean number (±SD) of PCA demands during the first 24 h after the operation was 105 (±88) for the IV-PCA group and 33 (±48) for the EPI-PCA group ($P < 0.01$). This difference was also significant 24–48 h after surgery. Although the EPI-PCA group utilized significantly less opioid medication, pain and sedation scores were similar in the two treatment groups; however, a significantly larger percentage of patients in the IV-PCA group (46% vs 22%) stated that they felt drowsy during the first postoperative day. Pruritus was reported more frequently in the EPI-PCA (67%) than in the IV-PCA (33%) group. Nausea was experienced by only 10% of patients in the IV-PCA and 6% in the EPI-PCA group. There was no evidence of postoperative respiratory depression, with minimal oxygen saturation values of 93% (±3%) and 94% (±1%) in the IV-PCA and EPI-PCA groups, respectively. The times to return of bowel sounds, resumption of solid diet, discontinuation of PCA therapy, and hospital discharge were significantly shorter in the EPI-PCA group ($P < 0.05$). In conclusion, EPI-PCA with hydromorphone appears to be a safe and effective alternative to conventional IV-PCA after cesarean delivery and offers the advantages of less opioid medication and a more rapid recovery.

(Anesth Analg 1992;75:245–51)

Patient-controlled analgesia (PCA) is a safe and effective technique for providing postoperative pain relief (1–3). Intravenous PCA (IV-PCA) has become a useful alternative to both intramuscularly and epidurally administered opioids after cesarean delivery (4–6). Early studies suggested that epidural opioid administration provided more effective analgesia with less medication compared with IV-PCA; however, conventional epidural opioid therapy is associated with the need for redosing and a high incidence of side effects (e.g., nausea, vomiting, pruritus, urinary retention) (4–15). Although the use of continuous epidural opioid infusions may obviate the need for redosing, it may obligate the patient to receive more opioid than is required (16) and increase the risk of respiratory depression (17). Epidural PCA (EPI-PCA) is a technique that combines the flexibility and convenience of PCA with the intrinsic analgesic efficacy of epidurally administered opioids (16–22).

Recent reports (23–25) suggest that the use of epidural opioids with a PCA delivery system may result in more rapid recovery and shorter hospital stay than conventional postoperative pain management techniques. The rapid-acting, lipid-soluble opioids (e.g., fentanyl, sufentanil, and alfentanil) have been used with EPI-PCA (17,19–22); however, the clinical advantages of administering these highly lipid-soluble opioids epidurally have been questioned because of the lack of a dose-sparing effect when compared with the intravenous route of administration (13,26–29).

This investigation was supported in part by a grant from Knoll Pharmaceuticals, Whippany, New Jersey.

This work was presented in part at the Annual Meeting of the Society of Anesthesiology, New Orleans, Louisiana, October 1989.

Accepted for publication March 31, 1992.

Address correspondence to Dr. White, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9068.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

We designed a prospective, randomized, controlled study to evaluate the safety and efficacy of epidural versus intravenous hydromorphone when administered with a PCA delivery system. The opioid analgesic requirements, quality of pain relief, patient satisfaction, side-effect profile, and recovery times were evaluated by using these two different PCA modalities after a standardized operation.

Methods

After written, informed consent was obtained, 117 adult women, ASA physical status I and II, scheduled to undergo elective cesarean delivery were randomly assigned to one of two PCA treatment groups. The study protocol was approved by the Washington University Human Studies Committee. The theoretical basis for PCA therapy and the operational aspects of the PCA device were explained to the patient at the time of the preoperative visit and were reviewed with each patient before initiating PCA therapy in the postanesthesia care unit. Patients with evidence of bacteremia or coagulopathy, as well as those who were reluctant to have an epidural catheter remain in place after their operation, were excluded.

All patients were given 15–25 mL of 0.5% bupivacaine via a percutaneous lumbar epidural catheter for surgical anesthesia. In five patients, fentanyl (50 μg IV) was required to supplement epidural analgesia immediately after delivery. On arrival in the postanesthesia care unit, a Bard Ambulatory PCA device was connected either to the patient's intravenous catheter (IV-PCA) or to her epidural catheter (EPI-PCA), according to random assignment. In the IV-PCA group, the device was programmed to deliver 1-mL (0.15 mg) hydromorphone bolus doses "on demand," with a minimal lockout interval of 10 min. In the EPI-PCA group, a loading dose of 6 mL (0.9 mg) of preservative-free hydromorphone (Dilaudid) was administered, and the device was programmed to deliver 1-mL (0.15 mg) supplemental hydromorphone bolus doses on demand, with a minimal lockout interval of 30 min. In addition to the number of delivered bolus doses, the number of demands (button presses) for supplemental medication was recorded during the 48-h study period. After 17 patients had been entered into the EPI-PCA group, the concentration of hydromorphone was decreased to 0.075 mg/mL, and the initial hydromorphone loading dose was decreased to 0.225 mg (3 mL) to minimize side effects associated with this technique (30). The supplemental hydromorphone bolus dose remained 0.15 mg (2 mL), and the lockout interval was unchanged. For purposes of statistical analysis, the EPI-PCA group was subdivided into phase I (hydromorphone loading dose of 0.9 mg) and phase II (hydromorphone loading dose of 0.225 mg).

Evaluation of postoperative respiratory status included respiratory rate (every 2 h by the ward nurses) and measurement of hemoglobin oxygen saturation (Spo_2) while patients were at bed rest with a Nellcor Oxinet pulse oximetry telemetry system. An alarm would sound at the nursing station when the Spo_2 decreased to <85%. Other postoperative assessments included hydromorphone utilization, PCA demands and boluses delivered, recovery times from completion of the operation to unassisted ambulation, return of bowel sounds (on auscultation), resumption of solid diet, and hospital discharge.

Patients assessed their pain and sedation levels at 8-h intervals using 100-mm linear visual analogue scales (from 0 = none to 100 = maximal) (31). All patients were evaluated by the primary care nurse at 2-h intervals, and opioid-related side effects (e.g., nausea, vomiting, dizziness, pruritus) were noted. Side effects were treated according to a standardized protocol if symptoms were present on successive nursing visits or if the patient complained of persistent symptoms. The PCA therapy was discontinued when patients tolerated a clear liquid diet. Postoperative PCA assessment questionnaires were completed by the patient as well as by her surgeon and primary care nurse after completion of the PCA therapy.

Opioid usage, pain and sedation scores, and recovery times were analyzed with one-way analysis of variance and a Bartlett's post hoc test to determine differences among the three groups (IV, EPI—phase I, EPI—phase II); χ^2 testing was used to analyze discrete variables. The Wilcoxon rank-sum (nonparametric) test was used to compare median values for visual analogue scores and number of bolus doses and demands in the three PCA treatment groups. Changes in opioid usage over time within each treatment group were evaluated with repeated measures of analysis of variance and Student's *t*-test with Bonferroni's correction. A P value <0.05 was considered statistically significant. Data are reported as medians (and interquartile ranges) or mean values ± SD (in tables) and ±SEM (in figures).

Results

One hundred seventeen women were enrolled in the study from November 1988 to December 1990. The three PCA treatment groups were comparable with respect to clinical variables (Table 1). The duration of surgery and total intraoperative epidural local anesthetic dosages were also similar in the three groups. One patient in each PCA group required the addition of supplemental (parenteral) medication to optimize

Table 1. Clinical Characteristics of Patients in the Intravenous and Epidural Patient-Controlled Analgesia Treatment Groups

	IV-PCA group (n = 49)	EPI-PCA groups	
		Phase I (n = 17)	Phase II (n = 41)
Age (yr)	28 ± 5	27 ± 6	28 ± 6
Height (cm)	163 ± 5	161 ± 7	162 ± 4
Weight (kg)	83 ± 24	83 ± 21	77 ± 12
Bupivacaine (mg)	138 ± 56	124 ± 67	110 ± 13
Operation (min)	71 ± 23	77 ± 35	64 ± 20

IV, intravenous; EPI, epidural; PCA, patient-controlled analgesia. Results are mean values ± SD.

postoperative analgesic therapy. The epidural catheter became dislodged, and PCA therapy was changed to IV-PCA in two patients in the phase I EPI-PCA group and in three patients in the phase II EPI-PCA group. In addition, three patients in the IV-PCA group and two patients in the phase II EPI-PCA group requested that PCA therapy be discontinued because of persistent opioid-related side effects. Data from these patients were included until the time of the protocol violation.

A comparison of the total hydromorphone utilization during the first 24 h after surgery revealed little difference between the phase I EPI-PCA group (1.8 ± 0.9 mg) and the phase II EPI-PCA group (2.1 ± 1.1 mg); however, the IV-PCA group required a significantly larger dose of hydromorphone (7.6 ± 2.7 mg) in the first 24 h than either of the EPI-PCA groups ($P < 0.01$). An analysis of PCA usage in each 4-h period in the first 24 h demonstrated consistently more opioid usage in the IV-PCA group than in the EPI-PCA groups after the initial 4-h period (Figure 1). Excluding the loading dose, patients in both EPI-PCA groups used similar doses in each 4-h period (Figure 1). For those patients requiring PCA therapy for 48 h, opioid usage remained significantly higher in the IV-PCA than the EPI-PCA groups during the second 24-h period. Of the patients enrolled in this study, 21 of 49 (43%) in the IV-PCA group required PCA therapy for at least 48 h after surgery, whereas 5 of 17 (30%) in the phase I EPI-PCA group and only 6 of 41 (14%) in the phase II EPI-PCA group required PCA therapy for the entire 48-h study period.

The number of PCA demands (button presses) in the first 24 h was significantly greater for the IV-PCA group (105 ± 88) than for either the phase I EPI-PCA group (14 ± 12) or the phase II EPI-PCA group (33 ± 48). The IV-PCA group demanded significantly more doses in the first 4-h period (13 ± 11) than the phase I EPI-PCA group (3 ± 4) but did not differ from the phase II EPI-PCA group (11 ± 29). Patients in the IV-PCA group demanded significantly more bolus doses in each of the remaining 4-h periods of the 48-h study period than patients in the two EPI-PCA groups (Figure 2A). The mean number of PCA demands during the second 24-h period was similar in the two EPI-PCA groups. As expected, the number of PCA demands exceeded the number of delivered doses in both the IV-PCA and EPI-PCA treatment groups (Figure 2); however, the ratio of delivered doses to demands in each of the 4-h intervals during the 48-h study period was significantly higher in the EPI-PCA groups (0.74–0.92 and 0.68–0.93 in phases I and II, respectively) compared with the IV-PCA group (0.57–0.76). The number of delivered bolus doses was also significantly higher ($P < 0.05$) in the IV-PCA group than in either of the EPI-PCA groups throughout the 48-h study period (Figure 2B).

Pain and sedation scores were similar throughout the study period in the IV-PCA and EPI-PCA groups (Figure 3). On the follow-up questionnaire, 18% of the IV-PCA-treated patients indicated that they had experienced moderate-to-severe pain after their operation versus only 5% of the EPI-PCA-treated patients. The nurses also reported similar findings on their follow-up questionnaires. Nevertheless, 92% of the IV-PCA group and 96% of the EPI-PCA groups felt that their pain had been adequately treated after surgery. Despite similar sedation analogue scores, a significantly greater percent of patients in the IV-PCA group (46%) felt drowsy during the first postoperative day compared with those in the EPI-PCA groups (22%).

On the follow-up patient questionnaire, very few patients felt that the pain medication caused nausea (10%, 12%, and 6% in the IV-PCA and phase I and phase II EPI-PCA groups, respectively). The symptoms of nausea during PCA therapy were reported by nurses in 5%, 29%, and 9% of patients in the IV-PCA and phase I and phase II EPI-PCA groups, respectively (Table 2). Pruritus was more common in the EPI-PCA groups (71% in phase I and 67% in phase II) than in the IV-PCA group (33%). Symptoms of pruritus were elicited by the ward nurses during PCA therapy in 33%, 61%, and 67% of patients in the IV-PCA and phase I and phase II EPI-PCA groups, respectively (Table 2). Pruritus requiring treatment was seen in 13% of the IV-PCA group and 51% of the phase I and 24% of the phase II EPI-PCA groups (Table 2). Urinary hesitancy (or the need to recatheterize the bladder) after initial bladder catheter removal was uncommon (Table 2). There were no complaints of dizziness during the study period.

The lowest Spo_2 (lasting > 2 min) during the 48-h study period was determined by using a printout from the Nellcor Oxinet telemetry system. The IV-PCA group had a mean (±SD) lowest Spo_2 of 93% (±3) versus 94% (±1) in the EPI-PCA groups. No

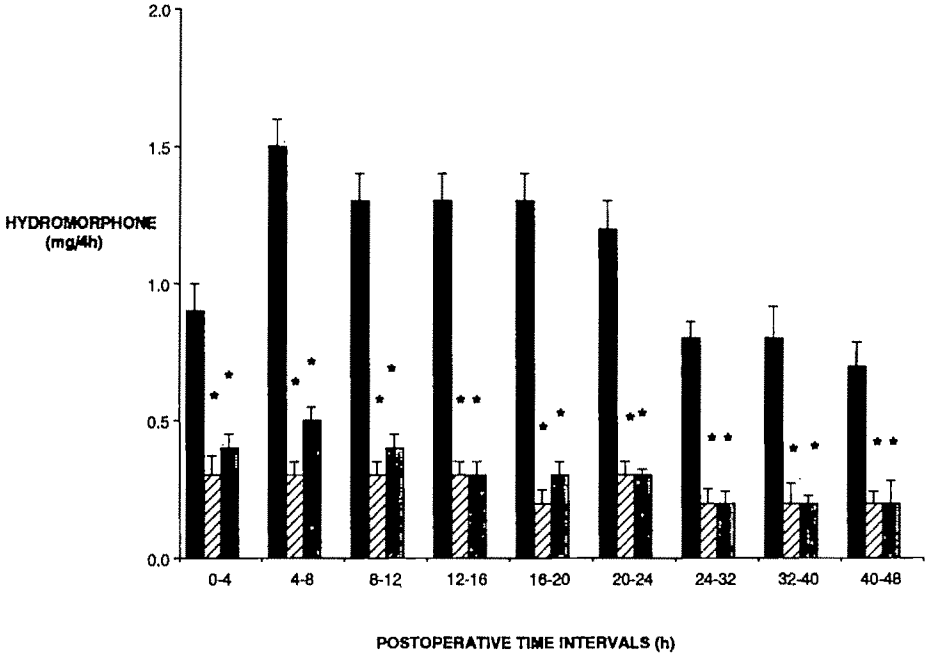


Figure 1. Postoperative hydromorphone utilization (mg/4 h) after the loading dose. *Solid bars*, IV-PCA group; *hatched bars*, EPI-PCA group (phase I); *stippled bars*, EPI-PCA group (phase II). Results are mean values ± SEM. *$P < 0.05$, significantly different from IV-PCA group.

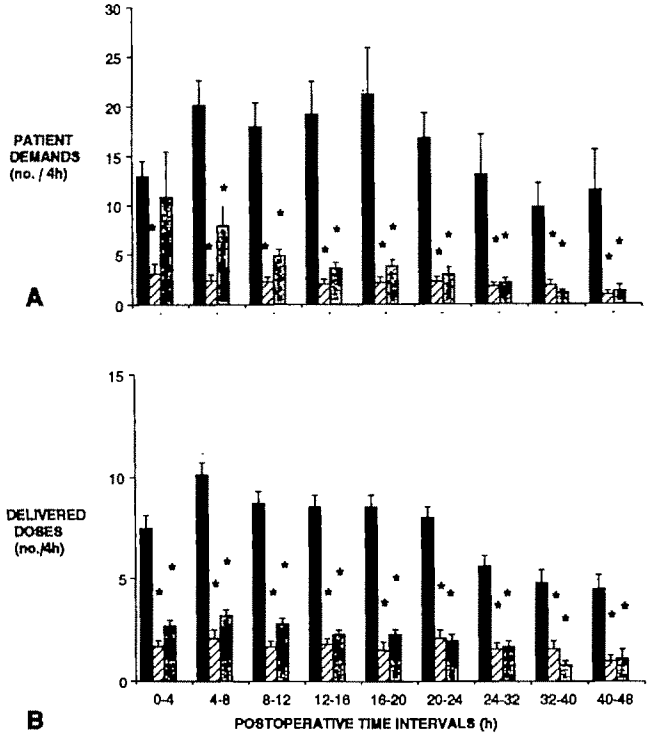


Figure 2. Postoperative PCA demands (**A**) and doses (**B**) per 4 h. *Solid bars*, IV-PCA group; *hatched bars*, EPI-PCA group (phase I); *stippled bars*, EPI-PCA group (phase II). Results are mean values ± SEM. *$P < 0.05$, significantly different from IV-PCA group.

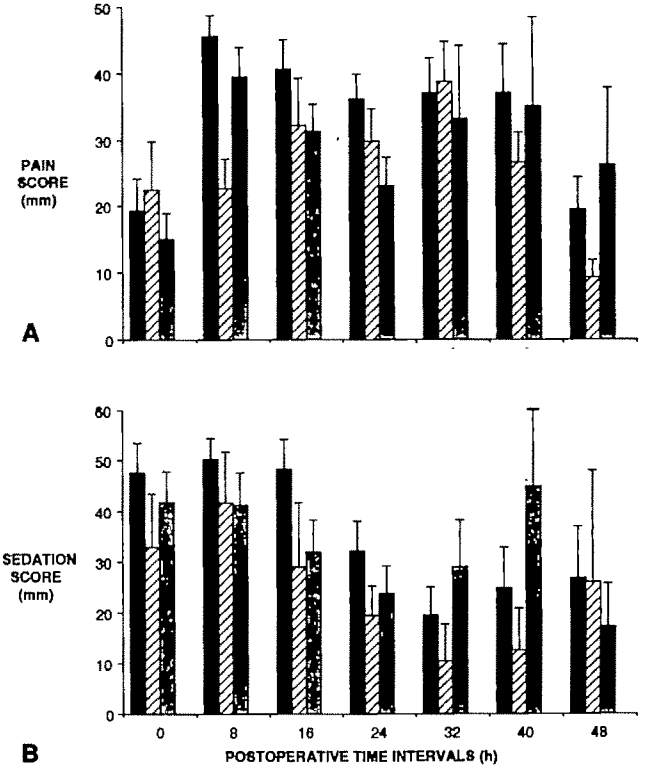


Figure 3. Postoperative pain (**A**) and sedation (**B**) analogue scores on a scale (mm) from 0 = none to 100 = maximal. *Solid bars*, IV-PCA group; *hatched bars*, EPI-PCA group (phase I); *stippled bars*, EPI-PCA group (phase II). Results are mean values ± SEM.

Table 2. Percent of Patients With Opioid-Related Side Effects in the Intravenous and Epidural Patient-Controlled Analgesia Treatment Groups as Reported by the Ward Nurses

	IV-PCA group (n = 48)	EPI-PCA groups	
		Phase I (n = 14)	Phase II (n = 37)
Nausea	5 (2)	29 (17)*	9 (0)
Vomiting	2 (2)	17 (11)	5 (5)
Pruritus	33 (13)	61 (51)*	67 (24)*
Excessive sedation	10 (0)	17 (0)	0 (0)
Urinary hesitancy	2 (2)	6 (0)	5 (0)

IV, intravenous; EPI, epidural; PCA, patient-controlled analgesia.
Number in parentheses indicates the percent of patients in each group requiring therapy for side effects.
*Significantly different from IV-PCA group; $P < 0.05$.

Table 3. Recovery Times for Patients in the Intravenous and Epidural Patient-Controlled Analgesia Treatment Groups

	IV-PCA group (n = 45)	EPI-PCA groups	
		Phase I (n = 14)	Phase II (n = 35)
Ambulation (h)	20 ± 7	26 ± 6	16 ± 5
Bowel sounds (h)	26 ± 15	24 ± 11	18 ± 9*
Solid diet (h)	59 ± 17	61 ± 22	49 ± 13*
Discontinue PCA (h)	40 ± 17	37 ± 13	31 ± 11*
Hospital discharge (h)	99 ± 21	98 ± 16	89 ± 16*

IV, intravenous; EPI, epidural; PCA, patient-controlled analgesia.
Results are mean values ± SD.
*Significantly different from IV-PCA group; $P < 0.05$.

patient in either EPI-PCA group had an Spo_2 value of <92%; however, four patients in the IV-PCA group had Spo_2 values ranging from 87% to 91%. Each of these patients was noted to have increased sedation scores at the time of their lowest Spo_2 value. In addition, these patients self-administered 1.5–2 times more hydromorphone than the average dose for patients in the IV-PCA group during the 4-h interval before their lowest Spo_2 value. All the episodes of low Spo_2 values (<90%) were self-limited and required no changes in PCA therapy.

The times to return of bowel sounds, resumption of solid diet, discontinuation of PCA, and hospital discharge were significantly longer in the IV-PCA group compared with the phase II EPI-PCA group (Table 3). On the surgeons' follow-up questionnaire, 44% of the patients were judged to be "ready for discharge" earlier than the surgeon had expected in the phase II EPI-PCA group (vs only 13% in the IV-PCA group [$P = 0.03$]). Oral analgesics were required sooner after the last dose of PCA-administered hydromorphone in the IV-PCA group (4 ± 8 h) compared with the phase I (14 ± 12 h) and phase II (7 ± 7 h) EPI-PCA groups.

Discussion

Patient-controlled analgesia can be utilized by a variety of routes of administration for the management of postoperative pain (32). Previous investigations of epidural PCA have been limited because of problems with study design (e.g., retrospective studies [23,24], historical controls [22], small patient populations with multiple surgical procedures [16], and by concomitant use of continuous opioid infusions with or without local anesthetics [17,19,21,26–28]). We evaluated the administration of epidural versus intravenous hydromorphone with a PCA device in a prospective, randomized, controlled manner in a large patient population undergoing the same surgical procedure. Thus, this controlled study compared two alternative routes of PCA administration.

Compared with epidural morphine, previous studies have suggested that epidural hydromorphone (a) is approximately 10 times more potent (33), (b) has a faster onset (13 ± 4 min vs 24 ± 6 min) (33), (c) has a shorter duration of analgesia (7 ± 1 h [34] or 11 ± 5 h vs 18 ± 7 h [33]), (d) provides comparable pain relief (12,14,16,33–36), (e) is safe even in a 10-fold overdose (36), and (f) may have fewer side effects (34). As the lipid solubility of hydromorphone is intermediate between morphine (low) and fentanyl (high), it should have a lower potential for rostral spread and resultant delayed respiratory depression than morphine and less potential for vascular (systemic) uptake than fentanyl.

Our data suggest that excellent pain relief and high patient satisfaction can be obtained with less opioid medication when patients self-administer hydromorphone by an epidural catheter (rather than the intravenous route). Despite reporting more pruritus, only 24% of the phase II EPI-PCA group required specific therapy (vs 13% of the IV-PCA group). The percent of patients in the two hydromorphone EPI-PCA groups requiring therapy for pruritus was lower than the percent (40%–45%) in epidural morphine studies involving the same patient population (4,5,13). More important, we found no evidence of clinically significant ventilatory depression in the EPI-PCA groups. In fact, the only patients with Spo_2 values <92% were receiving IV-PCA.

After the first 17 patients in the phase I EPI-PCA group had been entered into the study, we changed the epidural dosage because of the high incidence of side effects (Table 2). Twelve of the 17 patients (71%) reported pruritus and 5 reported nausea (29%) *within* the first 4 h after the initial hydromorphone loading dose. Because we considered the loading bolus dose

(0.9 mg) to be larger than necessary, we decreased the initial dose to 0.225 mg for the remaining phase II EPI-PCA patients. A comparison of opioid use in the first 24 h in the two EPI-PCA groups revealed similar total hydromorphone doses even though different loading doses were administered. With the availability of the PCA device, most patients were able to titrate the drug to the desired analgesic end point. By decreasing the loading dose, we were able to reduce the incidence of side effects associated with epidural hydromorphone without compromising its analgesic effectiveness.

Patients receiving the smaller loading dose of hydromorphone with EPI-PCA had a more rapid recovery of bowel sounds, earlier resumption of a normal diet, a shorter duration of PCA usage, and a decreased length of hospital stay compared with patients treated with conventional IV-PCA. This improved outcome was noted even though pain and sedation scores, as well as side-effect profiles, were similar in the IV-PCA and EPI-PCA groups. The most likely reason for the faster recovery variables relates to decreased opioid dosage associated with epidural (vs intravenous) administration.

Recently, Hongnat et al. (20) found comparable analgesia when alfentanil was administered by either EPI-PCA or IV-PCA in a small series of patients after gastrointestinal, urologic, vascular, or orthopedic surgery. Despite the dose-sparing effect, 10 of 13 EPI-PCA-treated patients had oxygen desaturation ($Spo_2 < 85\%$) compared with only 4 of 13 IV-PCA-treated patients. Glass and colleagues (29) reported that their prospective, double-blind, crossover study of EPI-PCA versus IV-PCA with fentanyl showed no differences in analgesia, plasma fentanyl concentrations, or cumulative fentanyl dosages. These authors concluded that the analgesic effects of epidural fentanyl appeared to be mediated primarily by systemic absorption. The present study would suggest that when hydromorphone is administered epidurally, it has more limited systemic absorption than fentanyl (29) and its newer analogues (13,20).

One potential problem with the use of EPI-PCA techniques relates to catheter migration or dislodgment, or both (37–40). Although there was no evidence of migration of the epidural catheter intravascularly or into the subdural (or subarachnoid) space, the catheter became spontaneously dislodged in 5 of the first 33 patients after ambulation. This problem was avoided in the remaining patients by securing the catheter with Benzoin spray, Steri-Strips, and a 4 × 10-in. Tegaderm dressing.

Limitations in our study design include (a) the lack of a double-blind protocol design, with the potential for biased evaluations on the part of the nurses and patients; (b) differing lockout intervals in the IV-PCA and EPI-PCA groups; and (c) the inability to extrapolate these results to other postsurgical patient populations. Even though investigator (and patient) bias could not be totally eliminated, the use of objective data and clinically relevant end points would minimize its impact on our results. Despite different lockout intervals, this was not the "rate-limiting" step in determining the number of successfully administered bolus doses in any of the PCA treatment groups. Future studies need to be performed in other surgical populations (i.e., after upper abdominal, thoracic, or joint replacement procedures).

In conclusion, EPI-PCA with hydromorphone is a safe and effective alternative to IV-PCA for providing pain relief after cesarean delivery. It remains to be determined whether the apparent safety and convenience of intermittent dosing with a PCA device connected to an epidural catheter offers any clinically significant advantages over physician-administered epidural injections in the management of acute postoperative pain.

The authors thank Linda Kratz, RN, for valuable assistance with data collection; Ian Smith, MD, for assistance in the preparation of the figures, Nellcor for the use of the Oxinet system, and Bard MedSystems Division (C. R. Bard, Inc., North Reading, Mass.) for the use of the Ambulatory PCA devices. Finally, the cooperation of our anesthesiologist, obstetrician, nursing, and pharmacist colleagues at Barnes Hospital was greatly appreciated.

References

1. Keeri-Szanto M, Heaman S. Postoperative demand analgesia. Surg Gynecol Obstet 1972;134:647–51.
2. Graves DA, Foster TS, Batenhorst RL, Bennett RL, Baumann TJ. Patient-controlled analgesia. Ann Intern Med 1983;99:360–6.
3. White PF. Use of patient-controlled analgesia for management of acute pain. JAMA 1988;259:243–7.
4. Eisenach JC, Grice SC, Dewan DM. Patient-controlled analgesia following cesarean section: a comparison with epidural and intramuscular narcotics. Anesthesiology 1988;68:444–8.
5. Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. Anesthesiology 1988;68:454–7.
6. Rayburn WF, Geranis BJ, Ramadei CA, Woods RE, Patil KD. Patient-controlled analgesia for post-cesarean pain. Obstet Gynecol 1988;72:136–9.
7. Reiz S, Westberg M. Side effects of epidural morphine. Lancet 1980;2:203–4.
8. Bromage PR, Camporesi EM, Durant PAC. Nonrespiratory side effects of epidural morphine. Anesth Analg 1982;62:490–5.
9. Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of epidural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982;1:479–85.
10. Findlay JWA, Butz RF, Teeple E, Ghia JN. Biphasic depression of ventilatory responses to CO_2 following epidural morphine. Anesthesiology 1983;58:418–27.
11. Abboud TK, Moore M, Zhu J, et al. Epidural butorphanol or morphine for the relief of post-cesarean section pain: ventilatory responses to carbon dioxide. Anesth Analg 1987;66:887–93.

12. Henderson SK, Matthew EB, Cohen H, Avram MJ. Epidural hydromorphone: a double-blind comparison with intramuscular hydromorphone for postcesarean section analgesia. Anesthesiology 1987;66:825–30.
13. Cohen SE, Tan S, White PF. Sufentanil analgesia following cesarean section: epidural versus intravenous administration. Anesthesiology 1988;68:129–34.
14. Dougherty TB, Baysinger CL, Henenberger JC, Gooding DJ. Epidural hydromorphone with and without epinephrine for post-operative analgesia after cesarean delivery. Anesth Analg 1989;68:318–22.
15. Palacios QT, Jones MM, Hawkins JL, et al. Post-caesarean section analgesia: a comparison of epidural butorphanol and morphine. Can J Anaesth 1991;38:24–30.
16. Marlowe S, Engstrom R, White PF. Epidural patient-controlled analgesia (PCA): an alternative to continuous epidural infusions. Pain 1989;37:97–101.
17. Boudreault D, Brasseur L, Samii K, Lemoing J. Comparison of continuous epidural bupivacaine infusion plus either continuous epidural infusion or patient-controlled epidural injection of fentanyl for postoperative analgesia. Anesth Analg 1991;73: 132–7.
18. Sjöström S, Hartvig D, Tamsen A. Patient-controlled analgesia with extradural morphine or pethidine. Br J Anaesth 1988;60: 358–66.
19. Ferrante FM, Lu L, Jamison SB, Datta S. Patient-controlled epidural analgesia: demand dosing. Anesth Analg 1991;73: 547–52.
20. Hongnat JM, Bellenfant F, Levy R, Alfonsi P, Chauvin M. Epidural versus intravenous alfentanil by PCA in postoperative patients (abstract). Anesthesiology 1991;75:A754.
21. Chrubasik J, Geller E, Graf R, Zbinden A, Thomson D. A double-blind comparison of epidural fentanyl and sufentanil with intravenous sufentanil for abdominal surgery pain management (abstract). Anesthesiology 1991;75:A752.
22. Grass JA, Zuckerman RL, Tsao H, Sakima NT, Harris AP. Patient-controlled epidural analgesia results in shorter hospital stay after cesarean section (abstract). Reg Anesth 1991; 16(Suppl 1):26.
23. Bellamy CD, McDonnell FJ, Colclough GW. Postoperative epidural pain management results in shorter hospital stay than IV PCA morphine: a comparison in anterior cruciate ligament repair (abstract). Anesthesiology 1989;71:A686.
24. Lamer TJ. Postoperative pain management with epidural narcotics results in shorter hospital stay than IV or IM narcotics (abstract). Reg Anesth 1990;15:83.
25. Guinard JP, Mavrocordatos P, Cuttat JF, Chiolero R. Shorter hospital stay with thoracic epidural fentanyl after thoracotomy (abstract). Anesthesiology 1991;75:A69.
26. Ellis DJ, Millar WL, Reisner LS. Comparison of epidural and intravenous fentanyl infusions after cesarean section (abstract). Anesthesiology 1989;71:A1153.
27. Panos L, Sandler AN, Stringer DG, et al. Epidural vs intravenous fentanyl infusions in postthoracotomy patients: analgesic and pharmacokinetic effects (abstract). Anesthesiology 1990; 73:A831.
28. Loper KA, Ready LB, Downey M, et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990;70:72–5.
29. Glass PSA, Estok P, Ginsberg B, Goldberg JS, Sladen RN. Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. Anesth Analg 1992;74:345–51.
30. Parker RK, Berberich N, Helfer DL, White PF. Use of epidural-PCA *versus* IV-PCA after obstetrical anesthesia (abstract). Anesthesiology 1989;71:A872.
31. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Med Psychol 1974;47:211–8.
32. White PF. Alternative routes for PCA in the management of acute pain. In: Ferrante FM, Ostheimer GW, Covino BG, eds. Patient-controlled analgesia. Boston: Blackwell, 1990:223–7.
33. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1990;59:473–80.
34. Shulman MS, Wakerlin G, Yamaguchi L, Brodsky JB. Experience with epidural hydromorphone for post-thoracotomy pain relief. Anesth Analg 1987;66:1331–3.
35. Horan CT, Beeby DG, Brodsky JB, Oberhelman HA. Segmental effect of lumbar epidural hydromorphone: a case report. Anesthesiology 1985;62:84–5.
36. Moon RE, Clements FM. Accidental epidural overdose of hydromorphone. Anesthesiology 1985;63:238–9.
37. Robson JA, Brodsky JB. Latent dural puncture after lumbar epidural block. Anesth Analg 1977;56:725–35.
38. Ravindra R, Albrecht W, McKay M. Apparent intravascular migration epidural catheter. Anesth Analg 1979;58:252–3.
39. Hatrick CT, Pither CE, Pai U, Raj PP, Tomsick TA. Subdural migration of an epidural catheter. Anesth Analg 1985;64:175–8.
40. Abouleish E, Goldstein M. Migration of an extradural catheter into the subdural space. Br J Anaesth 1986;58:1194–7.

PEDIATRIC ANESTHESIA
Section Editor
Paul R. Hickey

Alfentanil-Induced Rigidity in Newborn Infants

Marja-Leena Pokela, MD, Pauli T. Ryhänen, MD, Maila E. Koivisto, MD, Klaus T. Olkkola, MD, and Anna-Liisa Saukkonen, MD

Departments of Pediatrics and Anesthesiology, University of Oulu, Oulu, and Departments of Anesthesiology and Clinical Pharmacology, University of Helsinki, Helsinki, Finland

The authors evaluated whether alfentanil could be given before treatment procedures in critically ill mechanically ventilated neonates without adverse effects. Alfentanil (mean dose 11.7 μg/kg, range 9–15) was given intravenously to 20 mechanically ventilated critically ill newborn infants (mean birth weight 2510 g, range 1490–3990) during the first 3 days of life before treatment procedures. Heart rate, arterial blood pressure, transcutaneous partial pressure of O_2, respiratory rate, and general activity were observed continuously from 10 min before the administration of alfentanil until 1 h after it. Plasma alfentanil concentrations were measured in 15 subjects. The pharmacokinetics of alfentanil varied greatly among the subjects. The hemodynamic changes were not clinically significant, and the most important side effect was muscle rigidity. Nine infants had mild or moderate rigidity, which had little or no effect on ventilation. Four infants had severe rigidity and jerking comparable to convulsive activity, transiently impairing ventilation and oxygenation for approximately 5–10 min. Increased inspired oxygen and increased pressure by manual ventilation were needed to prevent hypoxemia. Electroencephalographic recordings for three infants during alfentanil administration showed no evidence of increased seizure activity. We conclude that alfentanil should not be used for newborn infants without simultaneous muscle relaxation because of the danger of rigidity.
(Anesth Analg 1992;75:252–7)

Increasing interest has recently been shown in the need for analgesia in newborn infants (1–5), even though the methods available for measuring pain in infants are limited. Some authors have, nevertheless, suggested that even preterm newborn infants have all the anatomic and physiologic components required for the perception of pain (6). Newborn infants with respiratory difficulties frequently become predisposed to hypoxemia and hazardous hemodynamic changes, such as a decrease in heart rate and an increase in arterial blood pressure and intracranial pressure, during even the most common treatment procedures, such as tracheal suction or the drawing of blood samples (7–10). Fluctuations in arterial blood pressure and hypoxemia in the preterm infant are associated with periventricular hemorrhagia and leukomalacia.

Opiates, such as morphine, meperidine, fentanyl, and alfentanil (11–14), have been used for the sedation of mechanically ventilated neonates. Marlow et al. (15) used alfentanil (20 μg/kg) and muscle relaxants for preterm infants during the first 4 days after birth and noticed a significant decrease in heart rate, arterial blood pressure, and oxygenation. Yet, Killian et al. (16) found that the administration of alfentanil (25 μg/kg) to newborn infants produced no significant changes in arterial blood pressure or heart rate. There are a number of reports of drug-induced rigidity and even seizures in adults during the induction of anesthesia with the rapidly acting opiates fentanyl, alfentanil, and sufentanil (17–19), but this has not been reported in neonates.

The purpose of this investigation was to evaluate whether alfentanil, given before treatment procedures, could be used in critically ill mechanically ventilated neonates to prevent hypoxemia and hazardous hemodynamic effects.

Methods

Institutional approval and informed consent from the parents was obtained to study 20 newborn infants. The entry criteria were that the trachea of the infants should be intubated and the lungs mechanically ventilated because of respiratory difficulties. Furthermore, they should be in a hemodynamically stable state with acceptable oxygenation and need analgesia or sedation for necessary treatment procedures. The

This work was supported by the Alma och K. A. Snellman Foundation and the Foundation for Paediatric Research in Finland.
Accepted for publication April 10, 1992.
Address correspondence to Dr. Pokela, Department of Pediatrics, University of Oulu, SF-90220 Oulu, Finland.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Clinical Characteristics of the 20 Mechanically Ventilated Neonates Given Alfentanil Intravenously

Pt No.	Wt (g)	Age (h)	Alfentanil dose (μg/kg)	Rigidity[a]	Treatment procedure	Diagnosis
1	1760	18	11	–	Tracheal suction	RDS
2	2650	25	15	+++	Blood sample	RDS
3	1690	38	12	++	Tracheal suction	RDS
4	2330	22	15	+++	Tracheal suction	RDS
5	2630	41	12	+	Chest x-ray, daily routine care	RDS
6	1710	16	15	++	Chest x-ray, daily routine care	RDS
7	3950	11	10	++	Tracheal suction	PFC
8	3240	51	10	–	IV cannulation	RDS
9	2930	24	10	–	Tracheal suction	Asphyxia
10	2130	6	10	+	Tracheal suction	RDS
11	1460	7	15	–	Tracheal suction	RDS
12	2400	8	11	+++	Tracheal suction	RDS
13	3170	28	10	–	Tracheal suction	Asphyxia
14	2160	20	9	++	Blood sample	RDS
15	2540	24	10	++	Tracheal suction	RDS
16	1830	26	15	+++	Radial artery cannulation	RDS
17	2670	18	10	++	EEG, daily routine care	RDS
18	2300	10	15	–	Radial artery cannulation	RDS
19	3190	38	10	+	EEG, daily routine care	Meconium aspiration
20	3320	19	11	–	EEG, daily routine care	Asphyxia

Pt, patient; RDS, respiratory distress syndrome; PFC, persistent fetal circulation; EEG, electroencephalography; IV, intravenous.
[a] –, No rigidity; +, mild rigidity; ++, moderate rigidity; +++, severe rigidity.

mean gestational age was 36 wk (range 30–40), mean birth weight 2510 g (range 1490–3990), and mean age at the time of the investigation 22.5 h (range 6–51). The clinical diagnosis was respiratory distress syndrome in 15 subjects, meconium aspiration syndrome in 1, persistent fetal circulation in 1, and asphyxia in 3 (Table 1).

A bolus dose of alfentanil (9–15 μg/kg IV) was administered over a period of 1 min before the treatment procedures, which entailed tracheal suction in 10 subjects, venous or arterial cannulation in 5, chest radiograph and daily routine care procedures, such as washing and weighing, in 2 and routine care procedures in 3. No other drugs were used.

Heart rate, respiratory rate, transcutaneous partial pressure of O_2 ($TcPo_2$), arterial blood pressure, and general activity were monitored continuously from 10 min before to 1 h after administration of alfentanil and were recorded before and at 2, 3, 5, 10, 30, and 60 min after administration. All observations were performed by the same investigator. Because rigidity and even convulsive activity were observed in some patients immediately after alfentanil administration, electroencephalographic (EEG) recordings were made in three infants 30 min before, during, and 30 min after the injection of alfentanil. One patient was given both alfentanil (10 μg/kg) and saline solution (placebo) in a blinded manner. Rigidity was graded in terms of passive resistance to movement of the limbs relative to the pretreatment level of resistance based on subjective impression according to the following four categories: no rigidity, muscle tonus unchanged or decreased; mild rigidity, slightly increased muscle resistance relative to pretreatment level; moderate rigidity, moderately increased muscle resistance relative to pretreatment level, with partly limited passive movements; and severe rigidity, greatly increased muscle resistance with totally restricted limb movements and involved convulsive activity such as jerking.

Arterial blood (1.5 mL) was sampled for the determination of alfentanil 0 (control), 2, 5, 10, 20, 60, 120, 240, and 360 min after injection in 15 cases. A maximum of five samples were drawn from any one patient. The samples were centrifuged and stored deep frozen until analyzed. Plasma concentrations of alfentanil were analyzed by capillary gas chromatography (20); the detection limit of the assay was 2 ng/mL. Arterial blood gas analysis was performed before and 1 h after alfentanil administration.

The terminal log-linear phase of the plasma con-

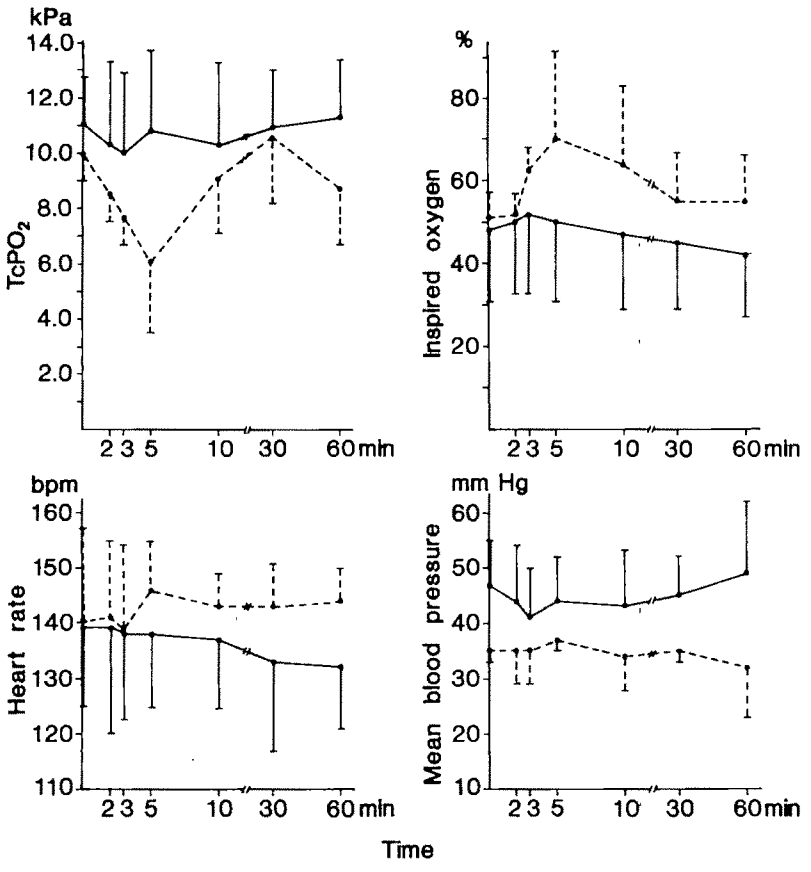


Figure 1. Physiologic responses to 9–15 μg/kg of alfentanil in patients without (*solid lines*, $n = 16$) and with (*dashed lines*, $n = 4$) severe rigidity. Results expressed as means ± SD. $TcPo_2$, transcutaneous partial pressure of O_2.

centration-time curve for each subject was identified visually. The elimination rate constant (k_{el}) was determined by regression analysis of the log-linear part of the curve. The elimination half-life ($T_{1/2}$) was calculated from $T_{1/2} = \ln 2/k_{el}$. The areas under the alfentanil concentration-time curves ($AUC_{0-\infty}$) were calculated using the linear trapezoidal rule when successive concentration values increased and the logarithmic trapezoidal rule when successive concentration values decreased after the peak concentration value. The area under the alfentanil concentration-time curve was extrapolated to infinity with the respective elimination rate constant value. Plasma clearance and steady-state volume of distribution of alfentanil were calculated using noncompartmental methods based on the statistical moment theory (21).

The hemodynamic effects of the alfentanil injection and acid-base status were analyzed using repeated measures analysis of variance over time, the nonparametric Wilcoxon rank-sum test, and the paired *t*-test with the SAS (Statistical Analyses System, Inc., Cary, N.C.). The pharmacokinetic parameters were compared with the Mann-Whitney U test. A P value <0.05 was considered statistically significant. The results are presented as means ± SD.

Results

There were no problems after alfentanil injection in 7 of 20 patients, slightly increased muscle tonus in 3 of 20, and a moderate increase in muscle resistance in 6 of 20 for whom ventilation was slightly aggravated but manual ventilation was not needed. The muscle resistance of 4 of 20 patients increased markedly; the range of passive movements was substantially limited; and myoclonic jerking suggestive of seizure activity was observed. When $TcPo_2$ decreased, manual ventilation was begun with an increased inspired O_2 concentration and increased pressure. The respiratory settings were not changed. Rigidity appeared immediately after alfentanil injection and before the beginning of the treatment procedure and disappeared within a few minutes. It had passed completely within 10 min (Figure 1). There was no correlation among the appearance of rigidity and gestational age, birth weight, and alfentanil dose or its maximal concentration (Table 1). Three of the patients who were given alfentanil twice showed similar rigidity on both occasions. An EEG was recorded in three patients, of whom two showed rigidity, including one who also had jerking and smacking

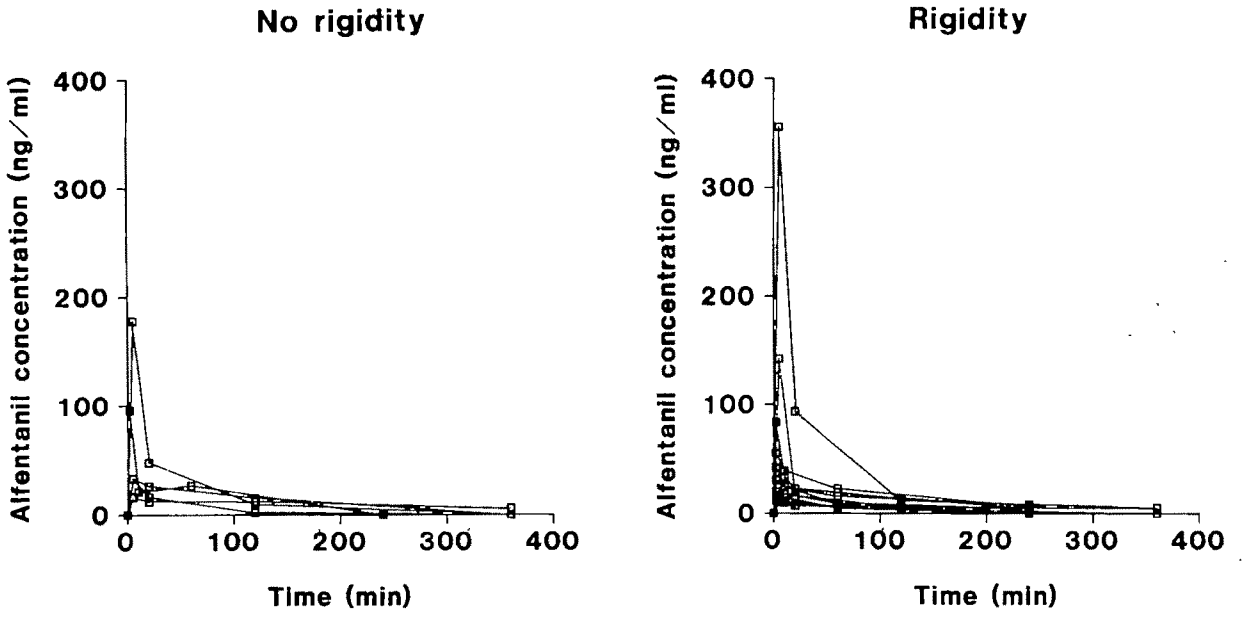


Figure 2. Alfentanil concentration after a single dose (9–15 μg/kg IV) in patients without rigidity and with rigidity.

immediately after the administration of alfentanil but not after a saline solution (placebo). No seizure activity was observed in the EEG during drug administration, but a progressive slowing in frequency (delta waves) and an increase in amplitude were seen. This periodic activity typical of opioid-induced sleep was observed in all three patients.

No major hemodynamic changes were seen. Mean arterial pressure and heart rate did not substantially change, and the only statistically significant difference was found in mean heart rate between the recordings made before and 60 min after medication (139 ± 14 vs 133 ± 11 beats/min; $P = 0.012$). Acid-base status did not differ between the arterial blood samples taken before alfentanil administration and 1 h afterward ($P = 0.100$) despite a transient decrease in $TcPo_2$ in the patients with severe muscle rigidity (Figure 1). There was a statistically significant difference in the amount of inspired O_2 5 min after the alfentanil injection in patients with severe rigidity ($P = 0.008$) compared with those not showing severe rigidity. The changes in the other variables were statistically insignificant (Figure 1).

Plasma alfentanil concentration profiles were determined for 15 patients; those for patients with and without muscle rigidity are depicted separately in Figure 2 and the respective pharmacokinetic parameters in Table 2. The highest alfentanil concentration was observed in a patient with muscle rigidity, but the pharmacokinetic parameters did not differ between the groups.

Table 2. Pharmacokinetic Variables of Alfentanil (9–15 μg/kg) After Intravenous Administration in Newborn Infants

	No rigidity ($n = 5$)	Rigidity ($n = 10$)
$T_{1/2}$ (min)	43 (34–237)	153 (31–650)
CL ($mL \cdot kg^{-1} \cdot min^{-1}$)	2.1 (1.7–7.2)	2.9 (0.9–25.3)
V_{ss} (L/kg)	0.27 (0.08–0.62)	0.66 (0.15–2.94)

$T_{1/2}$, elimination half-life; CL, plasma clearance; V_{ss}, volume of distribution at steady state.
Variables are given as median (range).

Discussion

Opiates can cause unexpected side effects in newborn infants because of immature hepatic and renal function and variable permeability of the blood-brain barrier. Data on the effects of various opiates on infants are still incomplete.

The pharmacokinetics of alfentanil have shown great individual variability in newborn infants (14,16,22). Our values for the pharmacokinetic variables differed slightly from those reported previously (14,16,22), partly because the small number of blood samples may have meant that the elimination phase was not described appropriately. This probably caused the values for elimination half-life to be lower and those for plasma clearance higher than the "true" ones.

No hemodynamic side effects such as decreases in arterial blood pressure or heart rate were seen in the infants. We used small doses (9–15 μg/kg) compared with Davis et al. (22) and Killian et al. (16), who gave

25 μg/kg of alfentanil to preterm and term infants to provide sedation during mechanical ventilation in the first 3 days without any significant hemodynamic changes. On the other hand, Marlow et al. (15) report a decrease in both heart rate and arterial blood pressure within 2 min after doses of 20 μg/kg of alfentanil given to premature infants (mean gestational age 30 wk). The gestational ages in the present series were higher (mean 36 wk). The patients were hemodynamically stable before the administration of alfentanil, and no other drugs were used. All of these factors might explain the difference.

Rigidity, the most significant adverse effect recorded here, appeared immediately after alfentanil injection and was intense, even convulsive, in 4 of the 20 infants. There are several reports of seizures and drug-induced rigidity in adults during the induction of anesthesia with fentanyl, sufentanil, and alfentanil (17–19), but no seizure activity has ever been reported in an EEG during these episodes. The movements often resembled seizures, involving stiffness of the limbs and trunk with explosive onset of myoclonic limb movements. Narcotic rigidity is usually thought to be dose related and to be noticeable only at large doses, but our results show that it can appear in neonates even after small doses. The pharmacokinetic parameters did not differ among our patients with and without muscle rigidity, and the EEG showed no seizure activity during alfentanil injection in any of the three cases in which recordings were made. The rigidity disappeared in a few minutes, but an increased inspired O_2 concentration and increased pressure by manual ventilation were needed to treat hypoxemia in the severe rigidity cases. Thus, the chest rigidity could predispose infants with hyaline membrane disease in particular to lung damage and pulmonary air leaks. We are unaware of any previous research carried out on this age group involving muscle rigidity.

Newborn infants with respiratory difficulties react to the most minor treatment procedures or maneuvers, even when painless, and most neonatal intensive care units will use some type of sedation, analgesia, and muscle relaxation during mechanical ventilation for stabilization. The use of neuromuscular blockers in neonates requiring mechanical ventilation is controversial, as noted by Costarino and Polin (23). Rigidity can undoubtedly be prevented by muscle relaxants, but although sedation with meperidine or morphine is used routinely at our hospital, relaxants are not, partly because they eliminate the clinical, neurologic, and externally observable reactions of the infants.

Alfentanil is a promising fast-acting drug for possible use in distressed, mechanically ventilated neonates during treatment procedures. The appearance of rigidity with the frequency described here after the use of such small doses of the drug nevertheless argues against its administration to newborn infants without simultaneous muscle relaxation. We have used alfentanil with suxamethonium and glycopyrrolate in connection with elective neonatal intubations without any serious adverse side effects.

The experience of pain or other stress associated with routine care can cause unwanted hemodynamic effects and hypoxemia in ill neonates; however, opiates can also cause adverse effects, one example of which is the rigidity described here. The appropriate dose required to reduce the stress experienced by mechanically ventilated infants during the various procedures necessary for their care and treatment has yet to be defined.

We thank the analytical department of Orion Pharmaceuticals for the measurements of plasma alfentanil concentration.

References

1. Yaster M. Analgesia and anaesthesia in neonates (editorial). J Pediatr 1987;111:394–5.
2. Editorial. Pain, anaesthesia, and babies. Lancet 1987;1:543–4.
3. Booker PD. Postoperative analgesia for neonates. Anaesthesia 1987;42:343–5.
4. Fletcher AB. Pain in the neonate. N Engl J Med 1987;317: 1347–8.
5. Fitzgerald M, McIntosch N. Pain and analgesia in the newborn. Arch Dis Child 1989;64:441–3.
6. Anand KJS, Phil D, Hickey PR. Pain and its effects in human neonate and fetus. N Engl J Med 1987;317:1321–9.
7. Perlman JM, Volpe JJ. Suctioning in the preterm infant: Effects on cerebral blood flow velocity, intracranial pressure, and arterial blood pressure. Pediatrics 1983;72:329–34.
8. Danfors DA, Miske S, Headley J, Nelson RM. Effects of routine care procedures on transcutaneous oxygen in neonates: a quantitative approach. Arch Dis Child 1983;58:20–3.
9. Marshall TA, Deeder R, Pai S, Berkowitz G. Physiologic changes associated with endotracheal intubation in preterm infants. Crit Care Med 1984;12:501–3.
10. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg 1987;66:874–8.
11. Bhat R, Chari G, Gulati A, Aldana O, Velamati R, Bhargava H. Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. J Pediatr 1990;117:477–81.
12. Miall-Allen VM, Whitelaw AGL. Effect of pancuronium and pethidine on heart rate and blood pressure in ventilated infants. Arch Dis Child 1987;62:1179–80.
13. Bell S, Ellis L. Use of fentanyl for sedation of mechanically ventilated neonates. Neonatal Network 1987 Oct:27–30.
14. Marlow N, Weindling AM, Van Peer A, Heykants J. Alfentanil pharmacokinetics in preterm infants. Arch Dis Child 1990;65: 349–51.
15. Marlow N, Weindling AM, Cooke RWI. Hazards of analgesia for newborn infants. Arch Dis Child 1988;63:1293.
16. Killian A, Davis PJ, Stiller RL, Cicco R, Cook DR, Guthrie RD. Influence of gestational age on pharmacokinetics of alfentanil in neonates. Dev Pharmacol Ther 1990;15:82–5.
17. Murkin JM, Moldenhauer CG, Hug CC, Epstein CM. Absence of seizures during induction of anesthesia with high-dose fentanyl. Anesth Analg 1984;63:489–94.

18. Smith NT, Benthuysen JL, Bickford RG, et al. Seizures during opioid anesthetic induction—are they opioid-induced rigidity? Anesthesiology 1989;71:852–62.
19. Benthuysen JL, Smith NT, Sandford TJ, Head N, Dec-Silver H. Physiology of alfentanil-induced rigidity. Anesthesiology 1986; 64:440–6.
20. Hynynen M, Takkunen O, Salmenperä M, Haataja H, Heinonen J. Continuous infusion of fentanyl and alfentanil for coronary artery surgery. Plasma opiate concentrations, haemodynamics and postoperative course. Br J Anaesth 1986;58: 1252–9.
21. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982.
22. Davis PJ, Killian A, Stiller RL, Cook DR, Guthrie RD, Scierka AM. Pharmacokinetics of alfentanil in newborn premature infants and older children. Dev Pharmacol Ther 1989;13:21–7.
23. Costarino AT, Polin RA. Neuromuscular relaxants in the neonate. Clin Perinatol 1987;14:965–89.

Preoperative Screening for Pediatric Ambulatory Surgery: Evaluation of a Telephone Questionnaire Method

Ramesh I. Patel, MD, and Raafat S. Hannallah, MD

Department of Anesthesiology, Children's National Medical Center, and the George Washington University School of Medicine and Health Sciences, Washington, D.C.

The purpose of this study was to determine whether preoperative screening of pediatric patients, accomplished by means of a preoperative telephone call to their parents, would decrease the rate of cancellation or postponement of ambulatory surgical procedures. Data from 5031 patients scheduled for ambulatory surgery were collected. During phase I of the study, when phone calls were attempted only during business hours, we contacted 805 of 1662 (48%) of patients' parents. The contact rate improved to 71% (2403 of 3369 patients) during phase II of the study, when phone calls were made in the evening, and parents were encouraged by the surgeons to call the ambulatory unit. Approximately 13% of the contacted parents reported a history of medical problems in their children. A preoperative anesthesia consultation was required in 2.8% of the patients whose parents were contacted. The rate of postponed or canceled surgery among those who could not be screened was 14.8%; among patients who were screened, it was 9.7% ($P < 0.001$). Patients in the former group were more likely than those in the latter group to require inpatient care for monitoring or treatment of underlying medical problems (1.3% vs 0.3%, respectively; $P < 0.05$). We conclude that a preoperative telephone interview is an effective method for screening pediatric ambulatory surgical patients.

(Anesth Analg 1992;75:258–61)

The growing popularity of ambulatory surgery has been largely dictated by social and fiscal considerations. Ambulatory surgery is especially suitable for children because many of the surgical procedures they commonly undergo are short and simple and because the patients are generally in good health (1). Thorough preoperative preparation and careful discharge planning are crucial to the success of an ambulatory surgical program. We cannot depend on the surgeon alone to evaluate and prepare the patient for anesthesia; this is especially true when a large number of surgeons practice at the same center (2). To ensure some degree of uniformity, the anesthesiologist must participate in preoperative screening or evaluation.

The purpose of this study was to determine the effect of a preoperative telephone screening program on the rate of cancellation or postponement of pediatric ambulatory surgical procedures.

Presented in part at the Annual Meeting of the Society for Ambulatory Anesthesia, San Antonio, Texas, April 1989.

Accepted for publication April 15, 1992.

Address correspondence to Dr. Patel, Department of Anesthesiology, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010.

Methods

Children's National Medical Center in Washington, D.C., provides comprehensive health care to children from a large metropolitan area. The ambulatory surgical unit is integrated into the main operating room. Surgeons select and schedule patients for ambulatory surgery in accordance with set guidelines under which ASA physical status I or II patients are considered appropriate candidates for ambulatory surgery. A consultation is requested before an ASA physical status III patient is scheduled for ambulatory surgery. A list of suggested ambulatory surgical procedures is provided to the surgeons and is updated periodically. Patients scheduled for ambulatory surgery are admitted through the AM Surgical Admission Center (AMSAC). After surgery and recovery room care, they are observed in the short-stay recovery unit until discharge.

Screening Procedure

The patient scheduled for ambulatory surgery undergoes a four-stage evaluation process. First, preoperative screening is accomplished by obtaining a detailed medical history by a directed telephone call

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

made through AMSAC 3–7 days before surgery. The AMSAC is staffed by a certified pediatric nurse practitioner (CPNP), a licensed practical nurse (LPN), and two admission clerks. The telephone calls are made by the CPNP during the day or by the LPN during the evening. The CPNP reviews all calls made by the LPN. A printed questionnaire designed to elicit information on anesthesia-related risk factors is used. Parents are asked specific questions about history of prematurity and cardiac, pulmonary, renal, endocrine, and other anesthesia-related risks.

If preexisting medical problems, such as history of prematurity or asthma, are discovered in the course of the telephone call, the case is reviewed by a staff anesthesiologist. When warranted by the medical history, the child is scheduled for an examination by the anesthesiologist a few days before surgery. Further consultations and tests are arranged according to the anesthesiologist's recommendations. The appropriateness of ambulatory surgery for these patients is reviewed, and surgeons are contacted if a change in admission status is contemplated.

A second telephone call is made to the parents on the evening before surgery by the evening-shift nurses of the short-stay recovery unit to detect acute illnesses. Such calls are made after 5 PM when the time required for direct patient care has decreased. During this call, the nurse inquires about acute illnesses, such as upper respiratory infection or diarrhea. Instructions about arrival time, fasting, and ambulatory care unit procedures are provided.

On the day of surgery, the patient is admitted through the AMSAC unit. The CPNP checks the patient in the AMSAC before starting the admission process. If the patient has any acute problems, such as fever or upper respiratory tract infection, or has violated fasting guidelines, a staff anesthesiologist is consulted before the admitting process is initiated.

The fourth and final step of the preanesthesia evaluation is the examination by the anesthesiologist. This is performed in an examination room adjacent to the play room (operating room holding area). The medical history is reviewed, and a physical examination is performed by the anesthesiologist. After the results of appropriate laboratory tests have been checked, anesthesia is induced.

Data Collection

A printed data sheet was completed for each patient as soon as surgery was scheduled. This form was used to follow the patient's course and note the final outcome. The final outcome was measured as completed surgery, canceled or postponed surgery, admission on the evening before surgery, or lost to follow-up. When parents were contacted for preoperative screening 3–7 days before surgery, the type of problems reported by the parents and action/consultation sought were noted.

During phase I of the study, we attempted to telephone parents during office hours (8 AM–4 PM). If that attempt was not successful, a second call was made on the following day. If we were unable to contact them on three consecutive days, no further attempts were made; parents of these patients were interviewed on the morning of surgery. Patients who could not be contacted by telephone, and therefore did not undergo the preoperative screening by the AMSAC unit 3–7 days before scheduled surgery, were placed in the "not contacted" group. During phase II, three changes were made in the screening process: first, calls to the parents were made during evening hours (4 PM–10 PM); second, a telephone answering machine was installed in the AMSAC so that parents could call and leave messages indicating when they would be available by telephone; and third, surgeons instructed parents to contact the ambulatory admission center if they did not receive the screening call.

The numbers and types of medical and nonmedical problems reported as a result of screening performed 3–7 days before surgery were analyzed. When a problem was discovered on the day of surgery, a decision was made to proceed with, postpone, or cancel surgery. When warranted, patients were admitted to the hospital before or after surgery for monitoring or treatment, or both.

The numbers of patients whose surgery was canceled or postponed or whose admission status was changed from ambulatory to in-hospital were compared with the patients who underwent the telephone screening process (3–7 days before surgery) and those who did not. The number of patients contacted during phase I was compared with the number of patients contacted during phase II. The results were compared with χ^2 analysis.

Results

A total of 5031 patients scheduled for ambulatory surgery were studied. During phase I of the study, we were able to contact 805 of 1662 consecutively scheduled patients (48%). The contact rate increased to 71% (2403 of 3369) during phase II of the study ($P < 0.0001$). Thirteen percent of the patients whose parents were contacted had a history of an underlying medical problem. On the basis of information obtained over the telephone, 2.8% (89) of the contacted patients were referred for an anesthesia consultation before the day of surgery. Even though the telephone screening was intended for medical pur-

Table 1. Problems Identified During Preoperative Telephone Screening for Pediatric Ambulatory Surgery

No. of patients (total)	5031
No. of screened patients	3208
Contact ratio[a]	
Phase I	805/1662 (48%)
Phase II	2403/3369 (71%)
Problems identified	
Medical (no.)	
History of prematurity	109
Cardiac	81
Asthma	52
Central nervous system	33
Other[b]	144
Total	419 (13.0%)
Socioeconomic	10 (0.3%)
Administrative (insurance documentation)	9 (0.3%)
Total	438 (13.6%)
Anesthesia consultation sought	89 (2.8%)

[a] $P < 0.0001$ (Phase I vs II).
[b] Less frequent conditions, such as Down's syndrome, gastrointestinal reflux, chronic ear infections.

Table 2. Outcome of Patients Who Were Contacted (Screened) Versus Those Who Could Not Be Contacted (Not Screened)

	Screened (n = 3208)	Not screened (n = 1823)
Surgery completed as scheduled	2529 (78.8%)	1300 (71.3%)
Surgery postponed/canceled[a]	311 (9.7%)	269 (14.7%)
Not rescheduled/lost to follow-up[b]	359 (11.2%)	231 (12.7%)
Change to PM admission (hospitalized the evening before surgery)[a]	9 (0.3%)	23 (1.3%)

[a] $P < 0.0001$.
[b] $P < 0.02$.

poses only, socioeconomic problems, such as lack of transportation or documentation of the custody of the child, were also discovered during the course of the telephone interview. Lapses in insurance documentation were also noted and corrected. Table 1 lists the medical and nonmedical problems discovered during the telephone screening process.

Table 2 lists the outcome of patients who were screened versus those who could not be screened. The rate of postponed or canceled procedures (versus those completed as scheduled) was approximately 50% higher in those who were not screened than in those who were screened (14.7% vs 9.7%, respectively; $P < 0.0001$). Patients in the unscreened group were also more likely be admitted to the hospital for postoperative monitoring or treatment of underlying medical problems, or both, than those who were screened (1.3% vs 0.3%, respectively; $P < 0.0001$).

Discussion

As ambulatory surgery is no longer limited to ASA physical status I or II patients undergoing superficial or minor procedures, the need for thorough preanesthetic screening has intensified. Our data support the importance of a formal screening process. Surgery was canceled or postponed more frequently in patients who were not screened than in those who were screened. Moreover, more patients in the group who could not be contacted needed overnight hospital admission than those who were contacted. Currently used methods for preanesthetic screening include personal interviews during a hospital visit, office or clinic consultation, telephone interviews, mail-in questionnaires, and computer-assisted questionnaires (3). Each method has its advantages and disadvantages for the parents and physician. The effectiveness of these various methods has not been objectively established and compared.

Telephone screening has several advantages, one of which is that the parents do not have to make an extra trip to the hospital. One of the drawbacks of telephone screening is that a physical examination cannot be performed by an anesthesiologist on all patients before the day of surgery. We believe that a good history can provide the clues needed to determine whether a physical examination before the day of surgery is necessary. If so, a preanesthetic visit can be arranged. In addition, all of our patients are examined by an anesthesiologist on the day of surgery before induction of anesthesia.

During the early part of this study, we gained information that helped us restructure our screening process. We realized that our contact rate during phase I was low because we were placing calls during the day, when most parents were at work. We changed our staffing pattern and started to contact parents in the evening. One part-time LPN was hired to complete the telephone calls during the evening. The expense was offset by an equivalent reduction in the daytime staff. Installation of an answering machine allowed parents to leave messages, telephone numbers, and times when they could be reached. Surgeons' office staff also instructed parents to initiate the call to our ambulatory unit to complete or schedule a telephone interview. These changes increased our contact rate from 48% to 71%. Our goal was to contact parents of all patients scheduled for surgery; nonetheless, last-minute scheduling by the surgeons and socioeconomic factors, such as lack of a telephone or difficulties in tracing guardianship of

foster care children and those living in shelter homes, made it impossible to reach all the families.

Surgery may still need to be postponed or canceled for patients who present to the ambulatory unit on the day of surgery with an acute problem, such as diarrhea, bronchitis, or upper respiratory tract infection, regardless of the thoroughness of the preoperative screening. A preoperative screening performed in advance will not detect such diseases. Even though the full fiscal impact of canceled or postponed surgical cases cannot be ascertained, such changes in the surgical schedule undeniably affect the efficient functioning of the operating room.

In conclusion, our results suggest that a comprehensive preoperative telephone interview is an effective method to identify anesthesia risk factors that may require preoperative intervention. Calling parents during the evening hours and encouraging them to call the ambulatory center enable the interviewer to contact more parents and thereby significantly improve the effectiveness of the prescreening process.

References

1. Hannallah RS, Epstein BS. The pediatric patient. In: Wetchler BW, ed. Anesthesia for ambulatory surgery. 2nd ed. Philadelphia: JB Lippincott, 1991:131–95.
2. Epstein BS, Hannallah RS. Outpatient anesthesia. In: Gregory GA, ed. Pediatric anesthesia. 2nd ed. New York: Churchill Livingstone, 1989:729–66.
3. Lutner RE, Roizen MF, Stocking CB, et al. The automated interview versus the personal interview. Anesthesiology 1991; 75:394–400.

Prolongation of Tetracaine Spinal Anesthesia by Oral Clonidine

Kouichi Ota, MD, Akiyoshi Namiki, MD, Yoshihito Ujike, MD, and Ikuko Takahashi, MD
Department of Anesthesiology, Sapporo Medical College and Hospital, Sapporo, Hokkaido, Japan

The effects of oral clonidine on the duration of isobaric tetracaine spinal anesthesia were studied in 30 patients undergoing urologic procedures. All patients received 15 mg of tetracaine intrathecally in isobaric saline solution. Group 1 (n = 10) received 0.25 mg of oral triazolam; group 2 (n = 10) received 0.15 mg of oral clonidine; and group 3 (n = 10) received 0.25 mg of oral triazolam and 0.75 mg of intrathecal phenylephrine. In group 1, the times for two- and four-segment regression of the level of analgesia to pinprick were 80 ± 17 and 123 ± 22 min, respectively (mean ± SD). The corresponding values of those measurements were 170 ± 27 and 273 ± 48 min in group 2 and 175 ± 34 and 273 ± 68 min in group 3. All the regression times in groups 2 and 3 were significantly longer than those in group 1. Regression times were not different between groups 2 and 3. The authors conclude that prolongation of tetracaine sensory analgesia may be produced by premedication with 0.15 mg of oral clonidine. The prolongation is similar to that produced by intrathecal phenylephrine.
(Anesth Analg 1992;75:262–4)

Clonidine decreases the minimum alveolar anesthetic concentration (MAC) of inhaled anesthetics (1,2) and the dose of narcotics required to prevent reflex cardiovascular response to tracheal intubation (3) and surgery (4). It also has potent analgesic properties in humans (5), and oral clonidine seems to be an effective premedication for general anesthesia (6,7). In addition, the intrathecal administration of clonidine is effective in prolonging spinal anesthesia with tetracaine (8,9) and bupivacaine (10,11). Pouttu et al. (12) reported that oral clonidine had the capacity to prolong the duration of bupivacaine spinal anesthesia; however, the capacity of oral clonidine to prolong tetracaine spinal anesthesia has not been established.

The present study was designed to assess the effect of oral clonidine premedication on the duration of tetracaine spinal anesthesia.

Methods

This study was performed in 30 male patients 20–65 yr of age, ASA physical status I or II, who were scheduled for cystoscopy and transurethral prostatic or bladder surgery with spinal anesthesia. All patients gave their informed consent after receiving a detailed explanation of the procedure, which was approved by the hospital ethics committee. The patients were randomly allocated to three groups. Group 1 (n = 10) received 0.25 mg of triazolam orally as premedication approximately 1 h before anesthesia. Group 2 (n = 10) was given 0.15 mg of clonidine orally approximately 1 h before anesthesia. Groups 1 and 2 received spinal anesthesia with 3 mL of 0.5% tetracaine in normal saline solution. Group 3 (n = 10) received 0.25 mg of oral triazolam 1 h before anesthesia and spinal anesthesia with 3 mL of 0.5% tetracaine in normal saline solution included with 0.75 mg of phenylephrine.

Immediately before the induction of anesthesia, an intravenous infusion of lactated Ringer's solution was started at a rate of 5–8 $mL \cdot kg^{-1} \cdot h^{-1}$. Arterial blood pressure was measured, and electrocardiogram lead II was recorded for measurement of heart rate. After recording control arterial blood pressure and heart rate, the patient was placed in a lateral recumbent position. Using aseptic technique, a lumbar puncture was performed with a 25-gauge needle at the L3-4 intervertebral space. Once a free flow of cerebrospinal fluid was obtained, the local anesthetic was injected at a rate of 1 mL every 3 s. After the injection, the patients were returned to the supine position and remained there for at least 20 min before being positioned for the operation. Dermatomal levels of sensory anesthesia were evaluated by pinprick. The

Accepted for publication March 31, 1992.
Address correspondence to Dr. Ota, Department of Anesthesiology, Sapporo Medical College and Hospital, W-16, S-1, Chyuou-ku, Sapporo, Hokkaido, 060, Japan.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Characteristics of Sensory Spinal Blockade in 30 Patients

	Oral triazolam (group 1, $n = 10$)	Oral clonidine (group 2, $n = 10$)	Oral triazolam + intrathecal phenylephrine (group 3, $n = 10$)
Maximal level of sensory blockade (dermatome)	T7.8 ± 1.5	T7.6 ± 1.8	T7.5 ± 1.7
Time to maximal level of sensory blockade (min)	24 ± 3	22 ± 6	27 ± 9
Time for two-segment regression (min)	80 ± 17	170 ± 27*	175 ± 34*
Time for four-segment regression (min)	123 ± 22	273 ± 48*	273 ± 68*
Time for regression to L-1 (min)	161 ± 43	312 ± 32*	329 ± 50*

L-1, first lumbar segment.
All values are mean ± SD.
*Significantly different from group 1 (Student's *t*-test); $P < 0.001$.

levels of pinprick analgesia were studied every 5 min for 30 min after the injection and were continued at intervals of 15 min until analgesia to pinprick recovered to the L-2 segment.

Arterial blood pressure and heart rate were monitored every 2 min for 10 min and every 10 min thereafter until the time of discharge from the recovery room. Hypotension (i.e., arterial blood pressure <90 mm Hg) was treated with either intravenous administration of fluid or ephedrine (5–10 mg).

All data are presented as mean ± SD. Statistical analysis was performed with Student's *t*-test and the Wilcoxon rank-sum test, with $P < 0.05$ taken to indicated a significant difference.

Results

The mean age, weight, and height of the 30 patients were 49 ± 15 yr, 62 ± 9 kg, and 165 ± 7 cm, respectively. These values were not significantly different among the groups. All surgical procedures were completed without complications.

The mean maximal levels of anesthesia (T-7–T-8) were similar in the three groups (Table 1). Although the times to maximal levels varied greatly in the three groups, ranging from 15 to 45 min, the mean values were not significantly different (Table 1). As shown in Table 1, the mean times from injection of the anesthetic to regression of the levels of sensory anesthesia by two segments varied from 80 to 175 min. There were significant differences in this variable between groups 1 and 2 ($P < 0.001$) and between groups 1 and 3 ($P < 0.001$). The mean regression times to four segments below the maximal levels were significantly prolonged by either administration of oral clonidine or intrathecal phenylephrine. Compared with group 1, the mean time for regression of the level of sensory anesthesia to L-1 was significantly longer in groups 2 and 3 ($P < 0.001$).

There were no significant differences in systolic arterial blood pressure before premedication and anesthesia in the three groups (Table 2). The lowest level of systolic arterial blood pressure during spinal anesthesia was not significantly different in the three groups.

Table 2. Systolic Arterial Blood Pressure and Heart Rate for Each Study Group

	Group 1 ($n = 10$)	Group 2 ($n = 10$)	Group 3 ($n = 10$)
SBP before premedication (mm Hg)	132 ± 18	128 ± 21	120 ± 15
SBP before anesthesia (mm Hg)	135 ± 20	121 ± 17	121 ± 15
Lowest SBP during spinal anesthesia (mm Hg)	115 ± 19	102 ± 7	106 ± 16
HR before premedication (beats/min)	80 ± 12	81 ± 10	79 ± 15
HR before anesthesia (beats/min)	82 ± 12	69 ± 9*	79 ± 16
Slowest HR during spinal anesthesia (beats/min)	70 ± 13	60 ± 10	71 ± 16
No. of patients requiring IV ephedrine	1/10	2/10	2/10

SBP, systolic arterial blood pressure; HR, heart rate.
All results are mean ± SD.
*Significantly different from group 1 (Student's *t*-test), $P < 0.05$, and significantly different from group 2 in heart rate before premedication (Student's *t*-test), $P < 0.05$.

As shown in Table 2, the heart rate before anesthesia in group 2 was significantly less than in group 1 ($P < 0.05$). The heart rate before anesthesia decreased significantly compared with that before premedication, but the slowest heart rate during spinal anesthesia was not significantly different among the three groups. The heart rate of any patient did not decrease to <50 beats/min at any time during this study.

Discussion

Our study shows that oral clonidine and intrathecal phenylephrine significantly prolonged the duration of tetracaine spinal anesthesia. When either oral clonidine or intrathecal phenylephrine was adminis-

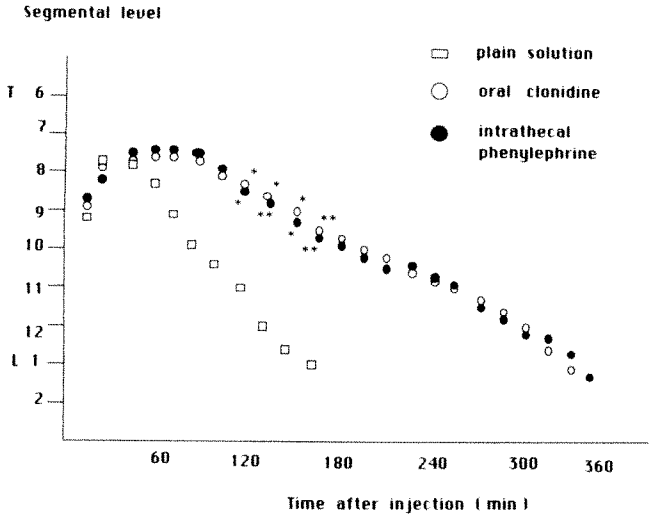


Figure 1. Mean segmental levels at various times after intrathecal administration of tetracaine in the three study groups. *Significantly different from group 1 (Wilcoxon rank-sum test); $P < 0.05$. **Significantly different from group 1 (Wilcoxon rank-sum test); $P < 0.01$.

tered, the percent of change from control duration of the time for regression to L-1 was almost doubled. In the prolonging effect of tetracaine spinal anesthesia, oral clonidine was similar to intrathecal phenylephrine (Figure 1).

Many investigators have found that phenylephrine and epinephrine significantly prolong sensory and motor blockade during tetracaine spinal anesthesia (13,14). Intrathecal clonidine, in a dose of 0.15 mg, prolongs tetracaine spinal anesthesia in dogs (15) and humans (9). Intrathecal clonidine also prolongs bupivacaine spinal anesthesia in humans (10).

The 0.15-mg oral dose of clonidine used in this study prolonged tetracaine spinal anesthesia in a similar fashion to phenylephrine. The oral dose of clonidine we used was approximately 2.4 μg/kg in all patients, similar to that (2.6 μg/kg) used for intrathecal administration in humans (9,10) in an attempt to prolong spinal anesthesia. However, this dose seems to be too small to elevate the concentrations of clonidine in cerebrospinal fluid. Clonidine is highly lipid soluble and crosses tissue barriers rapidly (16). We believe that the mechanism by which clonidine prolonged spinal anesthesia in this study was due to a supraspinal action; however, we have no data with regard to the concentration of clonidine in the blood and cerebrospinal fluid.

In conclusion, when utilized as premedication 0.15 mg of oral clonidine produced a clinically useful enhancement of the duration of tetracaine spinal anesthesia. When used in conjunction with tetracaine spinal anesthesia, oral clonidine premedication may have a distinct advantage because of its capacity to prolong sensory blockade and its potent sedating properties.

References

1. Kaukinen S, Pyykko K. The potentiation of halothane anesthesia by clonidine. Acta Anaesthesiol Scand 1979;29:107–11.
2. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 1982;61:741–5.
3. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirement of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986;64: 36–42.
4. Flacke JW, Bloor BC, Flacke WE, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987;67:11–9.
5. Tamsen A, Gordh TE. Epidural clonidine produces analgesia. Lancet 1984;2:231–2.
6. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 1987;67:3–10.
7. Pouttu J, Scheinin B, Rosenberg PH, Viinamaki O, Scheinin M. Oral premedication with clonidine: effects on stress responses during general anesthesia. Acta Anaesthesiol Scand 1987;31: 730–4.
8. Bedder MD, Kozody R, Palahniuk RJ, Cumming MO, Pucci WR. Clonidine prolongs canine tetracaine spinal anaesthesia. Can J Anaesth 1986;33:591–6.
9. Bonnet F, Brun-Buisson V, Saada M, Boico O, Rostaing S, Touboul C. Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. Anesth Analg 1989;68:619–22.
10. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987;66: 442–6.
11. Bonnet F, Diallo A, Saada M, Belon M, Guilbaud M, Boico O. Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 1989;63:93–6.
12. Pouttu J, Tuominen M, Scheinin M, Rosenberg H. Effects of oral clonidine premedication on concentrations of cortisol and monoamine neurotransmitters and their metabolites in cerebrospinal fluid and plasma. Acta Anaesthesiol Scand 1989;33: 137–41.
13. Conception M, Maddi R, Francis D, Rocco AG, Murray E, Covino BG. Vasoconstrictors in spinal anesthesia with tetracaine—a comparison of epinephrine and phenylephrine. Anesth Analg 1984;63:134–8.
14. Armstrong IR, Littlewood DG, Chambers WA. Spinal anesthesia with tetracaine—effect of added vasoconstrictors. Anesth Analg 1983;62:793–5.
15. Mensink FJ, Kozody R, Kehler CH, Wade JG. Dose-response relationship of clonidine in tetracaine spinal anesthesia. Anesthesiology 1987;67:717–21.
16. Timmermans PBMWM, Brands A, Van Zwietan PA. Lipophilicity and brain disposition of clonidine and structurally related imidazolidines. Arch Pharmacol 1977;300:217–26.

Continuous Low-Dose 3-in-1 Nerve Blockade for Postoperative Pain Relief After Total Knee Replacement

Neal D. Edwards, FCAnaes, and Eluned M. Wright, FCAnaes

Department of Anaesthesia, Morriston Hospital, Heol Maes Eglwys, Cwmrhydyceirw, Swansea, Great Britain

We have investigated the value of a 3-in-1 nerve block, followed by a continuous low-dose infusion of bupivacaine into the femoral nerve sheath for postoperative analgesia after total knee replacement. Thirty-seven patients were randomly allocated to either a control group or a study group. The study group had a catheter placed in the ipsilateral femoral nerve sheath. A 3-in-1 nerve block was then performed in the study group with injection of 30 mL of 0.25% bupivacaine through the catheter. This was followed by a continuous infusion of 0.125% bupivacaine at 6 mL/h. The study group had significantly lower pain scores 4 and 24 h postoperatively ($P < 0.01$) and required less postoperative opioid analgesic medication ($P < 0.01$) than the control group. The authors conclude that a continuous low-dose infusion into the femoral nerve sheath results in better pain relief than conventional intramuscularly administered narcotics after total knee arthroplasty.

(Anesth Analg 1992;75:265–7)

The technique of 3-in-1 neural blockade was first described by Winnie et al. (1) in 1973 and involves the injection of local anesthetic into the perineural sheath surrounding the femoral nerve to obtain blockade of the femoral nerve, obturator nerve, and the lateral cutaneous nerve of the thigh. It has been shown to be of value for analgesia after open knee surgery (2) and can be extended to provide continuous analgesia by insertion of a catheter into the femoral nerve sheath (3); however, previous studies used doses of bupivacaine approaching or exceeding the maximum recommended dose (4,5).

We have investigated the value of a 3-in-1 block achieved with a lower dose of bupivacaine, followed by a continuous low-dose infusion of bupivacaine into the femoral nerve sheath, as a method of pain relief after total knee replacement.

Methods

The study was approved by the hospital ethical committee, and written, informed consent was obtained from each patient. All patients undergoing total knee replacement under general anesthesia were considered eligible for the study. Patients with severe cardiorespiratory disease or hepatic or renal impairment were excluded.

All patients received a standard anesthetic. Premedication was temazepam (20 mg) 1 h before induction of anesthesia. Anesthesia was induced with intravenous fentanyl (1 μg/kg), thiopental (3–5 mg/kg), and vecuronium (0.1 mg/kg). The trachea was intubated and the lungs ventilated with oxygen, nitrous oxide, and isoflurane. Muscle relaxation was maintained throughout the operation with intermittent bolus doses of intravenous vecuronium. At the end of the procedure, neuromuscular blockade was reversed with intravenous neostigmine (2.5 mg) and glycopyrronium (0.5 mg).

Patients were prospectively randomized to one of two groups. The control group received no addition to the standard anesthetic. In the study group, after induction of anesthesia, a catheter was introduced into the ipsilateral femoral nerve sheath. Under aseptic conditions, the sheath was located with a Tuohy needle, with the double loss-of-resistance technique described previously by Khoo and Brown (6). A 16-gauge Portex epidural catheter was then passed through the Tuohy needle and secured with a standard dressing, so that 10 cm remained within the sheath. If on threading the catheter through the Tuohy needle it met with only minimal resistance, then the catheter was assumed to be correctly positioned. Initially, 30 mL of 0.25% bupivacaine was injected into the catheter to obtain a 3-in-1 block. This was immediately followed by an infusion of 0.125% bupivacaine at 6 mL/h, which was then continued

Accepted for publication March 31, 1992.

Address correspondence to Dr. Edwards, Department of Anaesthesia, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, Great Britain.

Reprints are not available.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

Table 1. Clinical Characteristics of 37 Patients Undergoing Total Knee Replacement

	Study group (n = 19)	Control group (n = 18)
Male/female	7/12	8/10
Mean age (SD) (yr)	66.9 (8.9)	65.6 (5.8)

Table 2. Postoperative Pain Scores (0 = no pain; 100 = worst pain imaginable) and Analgesic Requirements in 37 Patients

	Study group (n = 19)	Control group (n = 18)
Pain score at 4 h	32.9 (5.8)*	64.3 (5.2)
Pain score at 24 h	25.1 (4.3)*	55.6 (4.3)
Analgesia required in first 24 h		
No. of doses	1.32 (0–4)*	3.17 (2–4)
Total papaveretum dose (mg)	15.5 (0–55)*	43.0 (20–80)

Data are mean (SEM or range).
*Study group < control group; $P < 0.01$.

into the postoperative period for 24 h. After the operation, in both groups intermittent intramuscular papaveretum (10–20 mg every 4 h) was prescribed to be given on patient request.

Postoperative pain was assessed by a 100-mm visual analogue scale, which was completed by the patient at 4 and 24 h after the operation. In addition, the amount of postoperative opiate analgesia received by each patient in the first 24 h was noted. We did not assess loss of sensation in the distribution of the blocked nerves because of the presence of extensive dressings around the knee and thigh.

Patient pain scores and analgesic requirements were compared with the Mann-Whitney U-test.

Results

Forty-two patients initially participated in the study; 22 entered the study group and 20 the control group. In three patients in the study group, the femoral nerve catheters became dislodged before completion of the 24-h study period, and these patients were withdrawn from the study. Two patients in the control group did not complete the postoperative visual analogue scale, and these patients were also withdrawn, leaving 19 patients in the study group and 18 patients in the control group.

There were no significant differences between the groups with respect to age or gender (Table 1). The postoperative visual analogue scale pain scores and analgesic requirements are shown in Table 2. The pain scores of the patients in the study group were significantly lower than that of the patients in the control group at both 4 h ($P < 0.01$) and 24 h ($P < 0.01$). The patients in the study group required fewer doses of opiate analgesia than patients in the control group ($P < 0.01$). Six of 19 patients in the study group required no supplementary analgesia.

Discussion

Total knee replacement produces severe pain in 60% and moderate pain in 30% of patients (7). There are several methods available for providing postoperative analgesia, including systemic or epidural opiates and epidural local anesthetics. Opiates are associated with side effects, such as nausea, pruritus, and respiratory depression, whereas epidural local anesthetics may cause bilateral motor blockade (7), shivering, and hypotension.

The knee joint is innervated primarily by the femoral nerve but also receives branches of the obturator and sciatic nerves. The 3-in-1 technique will block the femoral and obturator nerves and has the advantage of causing no cardiovascular or respiratory side effects. The block is relatively easy to perform compared with other techniques of regional analgesia and does not require any special positioning of the patient. After knee surgery, postoperative pain can be associated with reflex spasm of the quadriceps muscle, causing further pain and impaired muscle function. Abolition of quadriceps muscle spasm by femoral nerve blockade contributes to the effectiveness of the technique. We saw no complications of the block in our patients, although prolonged femoral nerve blockade has been reported, either as a result of intraneural injection (8) or with high doses of local anesthetic (9). Injection of lower concentrations of local anesthetic through a catheter rather than a hypodermic needle, as in this study, should reduce the risks of this occurring.

Previous studies using a 3-in-1 block after knee surgery have used larger doses of bupivacaine. In a study of patients undergoing open knee surgery, Dahl et al. (4) found that a 3-in-1 block performed with 2 mg/kg of bupivacaine, followed by an infusion of bupivacaine into the femoral nerve sheath at 0.35 $mg \cdot kg^{-1} \cdot h^{-1}$, resulted in a significant reduction in postoperative pain; however, of 10 patients in the study group, 1 patient had a plasma bupivacaine concentration of 2.1 $\mu g/kg$ 30 min after the start of the infusion. In a recent study of patients undergoing total knee replacement, Misra et al. (5) combined a 3-in-1 block with a sciatic nerve block, resulting in effective postoperative analgesia; however, the total dose of bupivacaine given to each patient was 3 mg/kg, exceeding the manufacturer's

maximum recommended dose of 2 mg/kg. The peak plasma concentration in one patient reached 2 μg/mL.

The reported toxic concentration for bupivacaine is 2 μg/mL, although minor toxic symptoms have been described at an arterial concentration of 1.5–2.0 μg/mL (10). Although no patient in either of the studies by Dahl et al. (4) or Misra et al. (5) exhibited any clinical signs or symptoms of toxicity, the safety of the technique may be improved if analgesia can be obtained with a lower dose of local anesthetic.

In this study, we have used approximately half the dose of bupivacaine that has been used in previous studies, with a bolus dose of 75 mg of bupivacaine followed by an infusion of 0.125% bupivacaine at 6 mL/h. Pain scores were significantly lower compared with control patients at both 4 h and 24 h, as were 24-h opiate requirements. We have thus shown that a continuous low-dose infusion of bupivacaine into the femoral nerve sheath results in better pain relief after total knee replacement than a conventional intramuscular narcotic regimen, with minimal risk for bupivacaine toxicity.

The authors thank the Consultant Orthopaedic Surgeons at Morriston Hospital for allowing their patients to participate in the study, and Drs. P. A. Steane and D. Long for their encouragement.

References

1. Winnie AP, Ramamurthy S, Durrani Z. The inguinal perivascular technique of lumbar plexus anaesthesia: the 3-in-1 block. Anesth Analg 1973;52:989–96.
2. Tierney E, Lewis G, Hurtig JB, Johnson D. Femoral nerve block with bupivacaine 0.25% for postoperative analgesia after open knee surgery. Can J Anaesth 1987;34:455–8.
3. Rosenblatt RM. Continuous femoral anaesthesia for lower limb extremity surgery. Anesth Analg 1980;59:631–2.
4. Dahl JB, Christiansen JL, Daugaard JJ, Schultz P, Carlsson P. Continuous blockade of the lumbar plexus after knee surgery—postoperative analgesia and bupivacaine concentrations. Anaesthesia 1988;43:1015–8.
5. Misra U, Pridie AK, McClymont C, Bower S. Plasma concentrations of bupivacaine following combined sciatic and femoral 3-in-1 nerve blocks in open knee surgery. Br J Anaesth 1991; 66:310–3.
6. Khoo ST, Brown TCK. Femoral nerve block: the anatomical basis for a single injection technique. Anaesth Intensive Care 1983;11:40–2.
7. Rai P, Knarr D, Vigdodorlt E, Pither C. Comparison of continuous epidural infusion of local anaesthetic and administration of systemic narcotics in the management of pain after total knee replacement. Anesth Analg 1987;66:401–6.
8. Frerk CM. Palsy after femoral nerve block. Anaesthesia 1988; 43:167–8.
9. Madej TH, Ellis FR, Halsall PJ. Prolonged femoral nerve block with 0.5% bupivacaine. Anaesthesia 1988;43:607–8.
10. Reynolds FA. Comparison of the potential toxicity of bupivacaine, lignocaine and mepivacaine during epidural blockade for surgery. Br J Anaesth 1971;43:567–71.

Continuous Interpleural Infusion of Bupivacaine for Postoperative Analgesia After Surgery With Flank Incisions: A Double-Blind Comparison of 0.25% and 0.5% Solutions

Jack W. van Kleef, MD, PhD, E. Angelique Logeman, MD, Anton G. L. Burm, PhD, Jan Willem H. de Voogt, MSc, René A.G. Mooren, BSc, and Irene M. van Kleef-Mannot, MD

Department of Anesthesiology, Leiden University Hospital, Leiden, and Department of Anesthesiology, Sint Clara Ziekenhuis, Rotterdam, The Netherlands

Postoperative analgesia, as assessed by visual analogue scale scores (0–10) and patient-controlled analgesia morphine requirements, pulmonary function (forced vital capacity and forced expiratory volume in 1 s), and plasma bupivacaine concentrations were studied in patients receiving interpleural blockade with bupivacaine after surgery with a flank incision. Two groups of 10 patients received either 0.5% or 0.25% bupivacaine, both with epinephrine (5 μg/mL). Pain relief was initiated when patients had visual analogue scale scores ≥4. Patients received 21 mL of bupivacaine 0.25% or 0.5% in a double-blind fashion. One hour later, a continuous infusion of 5 mL/h of the study solution was started. At the same time, patient-controlled analgesia became accessible to the patients. The onset time of pain relief and the area under the visual analogue scale score-time curves over the first 8 h were similar in both groups. Patient-controlled analgesia morphine use was also similar in the 0.25% (21.3 ± 14.6 mg) and 0.5% (21.0 ± 16.0 mg) groups (mean ± SD). In both groups, forced vital capacity and forced expiratory volume in 1 s improved significantly within 60 min ($P < 0.05$). Peak plasma concentrations (C_{max}) and the area under the plasma concentration-time curve (AUC) over 24 h were higher ($P < 0.001$) in the 0.5% group (C_{max}, 1.47 ± 0.37 μg/mL; AUC, 1511 ± 323 $\mu g \cdot mL^{-1} \cdot min$) than those in the 0.25% group (C_{max}, 0.55 ± 0.22 μg/mL; AUC, 680 ± 118 $\mu g \cdot mL^{-1} \cdot min$) (mean ± SD). Plasma concentrations did not reach a plateau within 24 h, probably because of changes in protein binding: the degree of protein binding (95.9% ± 1.0% vs 92.4% ± 2.1%; $P < 0.001$) and plasma concentrations of α_1-acid glycoprotein (0.72 ± 0.16 g/L vs 0.57 ± 0.19 g/L; $P < 0.001$) (mean ± SD) were higher after 24 h than before the initial bolus injection. On the basis of this study, we recommend the use of the 0.25% solution for interpleural blockade.

(Anesth Analg 1992;75:268–74)

Besides intercostal (IC) administration, interpleural (IP) administration of a local anesthetic provides satisfactory pain relief after surgery with unilateral incisions (1–4). In a previous study (5), we demonstrated that the number of blocked dermatomes, as assessed by pinprick, was more variable after single-dose IP than after IC administration of 21 mL of 0.5% bupivacaine with epinephrine. Also, the mean time intervals from injection to two-dermatome regression and to first additional pain medication were shorter after IP than after IC administration. In addition, plasma concentrations of bupivacaine were significantly higher after IP than after IC administration, sometimes reaching levels generally considered potentially toxic. These results seem to favor the use of IC blockade. However, the relatively short and unpredictable duration of action that is seen after a single IP injection can be overcome by a continuous IP blockade technique, with either intermittent bolus injections or a continuous infusion.

Experience to date with continuous IP blockade is limited. Optimal dosage schemes, providing adequate postoperative analgesia and at the same time avoiding potentially toxic plasma concentrations of bupivacaine, have not been established. Therefore we compared the clinical effects and plasma concentration profiles after administration of a bolus dose of

This work was supported by ASTRA Pharmaceutica, Rijswijk, The Netherlands.

Accepted for publication April 10, 1992.

Address correspondence to Dr. van Kleef, Department of Anesthesiology, Leiden University Hospital, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

either a 0.25% or 0.5% bupivacaine solution, followed by a 23-h continuous infusion of the same solution, in patients undergoing a cholecystectomy or renal surgery with a flank incision.

Methods

The study was approved by the Committee on Medical Ethics of the Leiden University Hospital. Twenty consenting adult patients ranging in age from 20 to 65 yr and of ASA physical status I and II who had undergone renal surgery with a flank incision or a cholecystectomy (subcostal incision) were enrolled in the study. Patients with a history of traumatic or spontaneous pneumothorax, hemothorax, pleuritis with or without fibrosis, bullous emphysema, and allergy to local anesthetics were excluded from the study. Contraindications also included a history of drug abuse (precluding patient-controlled analgesia [PCA]). The patients were randomly assigned to one of two study groups to receive either 0.25% bupivacaine with epinephrine (5 μg/mL) (IP bupi 0.25%, $n = 10$) or 0.5% bupivacaine with epinephrine (5 μg/mL) (IP bupi 0.5%, $n = 10$). The PCA system was explained to the patients during the preoperative rounds.

The patients received premedication with temazepam (20 mg) and anesthetic induction with thiopental and succinylcholine for tracheal intubation. Anesthesia was maintained with fentanyl (0.1 mg) every 30 min, pancuronium, and enflurane in a nitrous oxide/oxygen (66%:33%) mixture.

After induction of general anesthesia, a 16-gauge catheter was introduced in the right jugular vein for central venous blood sampling. After closure of the surgical incision but before extubation, the patients were turned to the lateral decubitus position with the operated side uppermost, and ribs 12–8 were identified. A 16-gauge Tuohy needle with a freely moving air-filled glass syringe (5 mL) was then introduced into the IP space 10 cm from the posterior midline through the eighth or ninth IC space just above the rib. Technical details of the technique have been described elsewhere (2,5). After insertion and fixation of the catheter, patients were turned to the supine position and general anesthesia was terminated.

The degree of postoperative pain was evaluated by means of a visual analogue (VAS) scale for pain score at 10-min intervals. The VAS ranged from 0 (no pain) to 10 cm (excruciating pain). Postoperative pain relief was initiated in the recovery room when patients had VAS scores >4. Subsequently, a test dose of 3 mL of the study solution (0.25% or 0.5% bupivacaine with 15 μg of epinephrine) was injected. Two minutes later, in the absence of symptoms indicative of an intravascular injection, 18 mL of either 0.25% or 0.5% bupivacaine with epinephrine (5 μg/mL) was injected in a double-blind fashion (t = 0). One hour after the bolus injection, a continuous infusion of 5 mL/h of the test solution (bupivacaine 0.25% or 0.5%) was started. At the same time, PCA with morphine was started (PCA setting: bolus dose 3 mg; lockout period 25 min; no continuous infusion; morphine concentration 1 mg/mL).

The VAS scores and the number of dermatomes analgesic to pinprick were determined 2, 5, 10, 15, 20, 25, 30, 45 min and 1, 2, 3, 4, 6, 8, and 24 h after the initiation of pain treatment. Total PCA morphine use during the first 24 h was recorded. A bedside pulmonary function monitor was used to perform pulmonary function tests. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded on the day before surgery (in the absence of any pain), just before initiation of pain relief, and after 1, 6, and 24 h with the patient in a 30° semiseated position. The mean value of three assessments was recorded.

Central venous blood samples (5 mL) were collected before and 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, 960, 1200, and 1440 min after administration of bupivacaine. Plasma was obtained by centrifugation and stored at −20°C awaiting analysis.

The degree of protein binding of bupivacaine was determined in plasma samples collected before and 24 h after IP administration with equilibrium dialysis at 37°C (6). To this end, the sample collected before administration was spiked with 700 ng/mL of bupivacaine.

Concentrations of bupivacaine in 0.5-mL samples of plasma or dialysate were determined by capillary gas chromatography as described previously (7) with a few modifications: the HP 5890A gas chromatograph (Hewlett Packard, Palo Alto, Calif.) was equipped with a wall-coated open-tubular (WCOT) fused-silica column, length 12.5 m, internal diameter 0.32 mm, stationary phase: CP wax 57CB (Chrompack, Middelburg, The Netherlands), film thickness 0.2 μm, a nitrogen-selective detector, and a falling-needle solid injection system (Chrompack). Helium (4.5 mL/min) was used as the carrier gas. The temperatures of the oven, injection port, and detector were 215°, 300°, and 300°C, respectively. The retention times of bupivacaine and its *n*-pentyl homologue, which was used as the internal standard, were 2.6 and 3.2 min, respectively. The detection limit was <1 ng/mL, and the coefficient of variation in the range of concentrations encountered in this study did not exceed 5%.

Concentrations of α_1-acid glycoprotein and albumin in plasma samples collected before and 24 h after administration of bupivacaine were determined by

rate nephelometry with the Beckman Array Protein System (Beckman Instruments Inc., Fullerton, Calif.).

Statistical analysis of frequently collected serial data (VAS scores, number of blocked dermatomes, plasma concentrations) was done by analysis of relevant summary parameters derived from the raw data (8).

Areas under the VAS score-time curves (AUC) and under the number of blocked dermatomes-time curves over the first 8 h (AUC_{0-8}) and under the plasma concentration-time curves over 24 h (AUC_{0-24}) were determined with the trapezoidal rule.

Demographic data (age, weight, height), duration of surgery, and morphine requirements over 24 h were analyzed by the two-sample *t*-test. The Fisher exact test was used for comparison of frequencies (gender, ASA classification).

The VAS scores before the initiation of pain treatment, the time to onset of pain relief (from initiation of pain treatment until a VAS score ≤2 was obtained), AUC_{0-8} under the VAS score-time curves, and VAS scores 24 h after initiation of pain treatment were analyzed with the Mann-Whitney U test, as were the AUC_{0-8} under the number of blocked dermatomes-time curves and the number of blocked dermatomes 24 h after initiation of pain treatment.

Preoperative FVC and FEV_1 data were analyzed by the two-sample *t*-test. Postoperative FVC and FEV_1 data were analyzed with repeated measures analysis of variance, followed by the Newman-Keuls test.

Peak plasma concentrations (C_{max}), the times at which they were reached (t_{max}), and AUC_{0-24} under the plasma concentration-time curves were analyzed with the two-sample *t*-test. Percents of protein binding and plasma protein concentrations in samples collected before and 24 h after initiation of IP blockade were compared with the paired-sample *t*-test.

Data are presented as mean ± SD, median (range), or frequencies; $P < 0.05$ was considered statistically significant.

Results

No significant differences in patient characteristics existed between the groups (Table 1). One patient in each group had undergone renal surgery with a right flank incision; the remaining patients had undergone a cholecystectomy.

The median (range) number of analgesic dermatomes gradually increased during the first hour to 4 (3–7) dermatomes in the IP bupi 0.25% group and 6 (3–8) dermatomes in the IP bupi 0.5% group. In the IP bupi 0.25% group, the median number of blocked dermatomes showed an additional increase to 5.5 (3–8) dermatomes at 8 h. In the IP bupi 0.5% group, the median number of blocked dermatomes remained constant between 1 and 8 h. The AUC_{0-8} values were somewhat smaller in the IP bupi 0.25% group (median 40, range 23–53 dermatomes·h) than in the IP bupi 0.5% group (median 47, range 31–59 dermatomes·h; $P < 0.05$). The number of blocked dermatomes after 24 h also was smaller in the IP bupi 0.25% group (median 4, range 2–6 dermatomes) than in the IP bupi 0.5% group (median 7, range 0–8 dermatomes; $P < 0.005$).

Median VAS scores over the first 8 h are shown in Figure 1. Derived data are presented in Table 2. The VAS scores before the initiation of pain relief, onset time to VAS score ≤2, AUC_{0-8} values, and VAS scores after 24 h were not different between the groups. The PCA morphine requirements over the first 24 h also did not differ between the groups (Table 2).

Preoperative FVC and FEV_1 values were comparable in the two groups. Preoperative values of FVC were 3.41 ± 0.95 L in the IP bupi 0.25% group and 3.38 ± 0.42 L in the IP bupi 0.5% group. The corresponding values of FEV_1 were 2.74 ± 0.79 L and 2.79 ± 0.52 L, respectively. Postoperative FVC and FEV_1 data over time, expressed as percent of the

Table 1. Patient Characteristics and Duration of Surgery

	IP bupi 0.25% group (n = 10)	IP bupi 0.5% group (n = 10)
Age (yr)	41 ± 10	41 ± 14
Weight (kg)	74 ± 8	77 ± 16
Height (cm)	173 ± 8	172 ± 8
Gender (M/F)	4/6	4/6
ASA physical status (I/II)	8/2	3/7
Duration of surgery (min)	106 ± 54	121 ± 37

IP bupi, interpleural bupivacaine; M, male; F, female.
Data are mean ± SD or proportions, as appropriate.

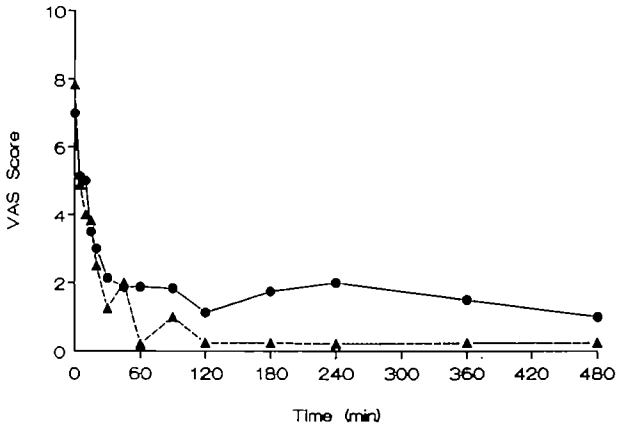


Figure 1. Median visual analogue scale (VAS) scores versus time over the first 8 h in the IP bupivacaine 0.25% (*circles*) and 0.5% (*triangles*) groups.

Table 2. Patient-Controlled Analgesia Morphine Requirements and Visual Analogue Scale (VAS) Scores

	IP bupi 0.25% group (n = 10)	IP bupi 0.5% group (n = 10)
Morphine requirement (mg/24 h)	21.3 ± 14.6	21.0 ± 16.0
VAS score		
Initial VAS score (cm)[a]	7.0 (5–10)	7.8 (4–10)
Onset time to VAS ≤2 (min)	30 (5–120)	25 (5–480)
AUC_{0-8} (cm·h)	15 (2–32)	5 (2–28)
VAS score after 24 h (cm)	3.8 (0–6)	0.5 (0–8.5)

IP bupi, interpleural bupivacaine; AUC_{0-8}, area under the VAS score-time curve over the first 8 h after initiation of pain relief.
Data are mean ± SD or median (range), as appropriate.
[a]VAS score just before the initiation of pain relief.

Table 3. Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 s (FEV_1) Before (t = 0) and 1, 6, and 24 h After Initiation of Pain Relief

Time (h)	IP bupi 0.25% group (n = 10)	IP bupi 0.5% group (n = 10)
FVC		
0	36 ± 19	33 ± 15
1	48 ± 22[a]	56 ± 15[a]
6	46 ± 15[a]	47 ± 14[a]
24	43 ± 15[a]	56 ± 15[a]
FEV_1		
0	34 ± 16	31 ± 15
1	47 ± 22[a]	57 ± 18[a]
6	47 ± 15[a]	49 ± 10[a]
24	45 ± 14[a]	58 ± 18[a]

IP bupi, interpleural bupivacaine.
Data (mean ± SD) are expressed as percent of the preoperative values.
[a]Difference with value before initiation of pain relief (t = 0), $P < 0.05$.

preoperative values, are presented in Table 3. The FVC and FEV_1 versus time profiles were similar in both groups. A significant improvement was observed 1 h after the bolus injection ($P < 0.05$). Thereafter, FVC and FEV_1 did not change with time (6 and 24 h).

Mean plasma concentrations as a function of time are shown in Figure 2. Pharmacokinetic data are presented in Table 4. Peak plasma concentrations (C_{max}) in the IP bupi 0.5% group were significantly higher than those in the IP bupi 0.25% group. Peak plasma concentrations were attained at the same time in both groups. The AUC_{0-24} values were approximately twice as high after IP bupivacaine 0.5% than after IP bupivacaine 0.25% administration. Peak plasma concentrations, and AUCs normalized for dose were similar in both IP study groups. Although the IP infusion was continued for 24 h, plasma concentrations did not reach a steady-state level.

In all patients receiving IP blockade with bupivacaine, the degree of protein binding was higher after 24 h (95.9% ± 1.0%) than before the administration of bupivacaine (92.4% ± 2.1%; $P < 0.001$). Plasma concentrations of α_1-acid glycoprotein were also higher (0.72 ± 0.16 g/L vs 0.57 ± 0.19 g/L; $P < 0.001$), whereas albumin concentrations were lower (29.4 ± 3.7 g/L vs 33.7 ± 2.8 g/L; $P < 0.001$) after 24 h than before the initial bolus injection.

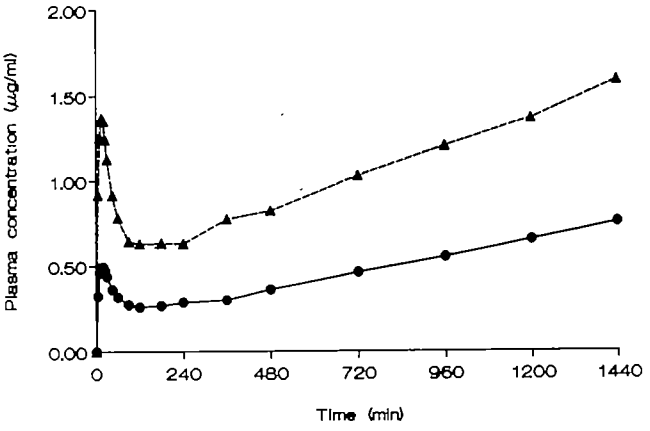


Figure 2. Mean plasma concentrations versus time over 24 h in the IP bupivacaine 0.25% (*circles*) and 0.5% (*triangles*) groups.

Table 4. Pharmacokinetic Variables in the Two Study Groups

Variable	IP bupi 0.25% group (n = 10)	IP bupi 0.5% group (n = 10)
C_{max} (μg/mL)	0.55 ± 0.22	1.47 ± 0.37[a]
t_{max} (min)	17.5 ± 6.8	16.7 ± 6.6
AUC_{0-24} (μg·mL^{-1}·min)	680 ± 118	1511 ± 323[a]

IP bupi, interpleural bupivacaine; C_{max}, central venous peak plasma concentrations; t_{max}, corresponding peak times; AUC_{0-24}, area under the plasma concentration-time curve over 24 h.
Data are mean ± SD.
[a]Difference between interpleural bupivacaine 0.25% and 0.5% groups; $P < 0.001$.

Discussion

Interpleural analgesia, first described in 1986 (9), has since rapidly captured the imagination of various groups as a major anesthetic technique (10). In ongoing research, different groups have studied the site of neural blockade (11) and have compared nerve block characteristics after IP administration of bupivacaine with those obtained after intercostal (5,12) or epidural blockade (1). There is also continued debate on the optimal dosage, volume, and concentration of the local anesthetic solution that on the one hand will result in reliable pain relief and on the other hand will not result in (potentially) toxic plasma concentrations.

The present study compared in a double-blind fashion two continuous IP regimens, using either 0.25% or 0.5% bupivacaine with epinephrine. The efficacy of IP blockade was determined with VAS scores and supplemental morphine requirements. The PCA morphine consumption is often used as a means of quantifying the efficacy of other analgesic regimens. A distinct advantage is that patients are offered an alternative should the evaluated regimen not offer adequate analgesia; however, the optimal PCA settings in such studies have not been established (13). In three other studies, where PCA was included to evaluate the efficacy of IP blockade (3,14,15), bolus dosages and lockout intervals were 1–2 mg with lockout times of 3–5 min, with a maximum PCA morphine dosage of 10 mg/h in one study (3). Although our PCA setting was aimed at maintaining an acceptable level of analgesia with minimal sedation and side effects, one may criticize this regimen as being conservative; however, the actual need for supplemental PCA dosages was far below the maximum dosage (174 mg) that patients were allowed during the study period.

Until now, in studies focusing on IP postcholecystectomy pain relief for periods varying from 24 to 48 h, bolus regimes of 0.5% bupivacaine (every 4–6 h) have been used predominantly (4,14,16). In an open study by Laurito et al. (15), it was shown that continuous IP infusion of 0.25% bupivacaine (0.125 $mL \cdot kg^{-1} \cdot h^{-1}$) during 24 h after cholecystectomy provides safer and more effective postoperative pain relief than intermittent IP injection of 0.5% bupivacaine (0.4 mL/kg) every 6 h. The present study compared (in a double-blind setup) the efficacy of continuous IP blockade with either 0.25% or 0.5% bupivacaine given as a bolus injection followed by a continuous infusion during 24 h. Both regimes resulted in rapid and effective pain relief.

Our findings and those by Laurito et al. (15) refute statements made by other investigators (14) that continuous IP infusion techniques may be less effective than intermittent IP bolus injections in relieving postcholecystectomy pain. In fact, morphine requirements in patients receiving IP blockade in this study (IP bupi 0.25% group: 21.3 ± 14.6 mg; IP bupi 0.5% group: 21.0 ± 16.0 mg) were similar to those reported by Lee et al. (14) who used injections of 20 mL of 0.5% bupivacaine every 4 h (mean 21.6 mg). The latter study showed a comparable reduction in PCA morphine requirements and in VAS scores compared with patients given morphine only. In the study by Laurito et al. (15), the PCA morphine requirement averaged 23 ± 5 mg in patients receiving a continuous infusion regimen of 0.25% bupivacaine. Among the patients receiving bolus injections of 0.5% bupivacaine, PCA morphine averaged 30 ± 15 mg during the 24-h study period.

Although several studies including the present one have demonstrated the efficacy of prolonged IP blockade in reducing the intensity of postcholecystectomy pain, supplementary PCA requirement is still of considerable magnitude (4,14–16). One possible explanation may be that patients often experience pain on the contralateral side, even when the surgeon did not cross the midline with the skin incision. A contributing factor may be that different nerve pathways are involved in the innervation of the upper abdomen, including phrenic, somatic, and visceral nerve afferents, some of which may not be blocked.

The improvement in pulmonary function observed 1 h after initiation of IP blockade in this study is consistent with observations reported by others (3,4,14,17). This observed improvement is probably related to the effective postoperative pain relief. During prolonged IP blockade, further improvements in pulmonary function after 1 h are either absent (this study) or insignificant (14,16). A detailed interpretation of the time-course of FVC and FEV_1 is hampered by factors such as the effects of surgery and of interpleurally administered local anesthetics (3,18) and the depressant effects of opioids, which may all influence pulmonary function.

One concern with any regional anesthetic technique requiring large doses of local anesthetic is the potential of these agents to elicit systemic toxicity (19). Estimates of the threshold plasma concentrations of bupivacaine associated with central nervous system toxicity in humans vary from 2 to 4 μg/mL (20). Plasma concentrations measured after IP injection of bupivacaine vary widely among studies, but several investigators have reported peak plasma concentrations that exceeded 2 μg/mL in at least some of their patients (5,21–23). Similar high plasma concentrations have also been obtained during prolonged continuous infusion of bupivacaine in patients after thoracotomy (24) and during intermittent bolus injections after cholecystectomy (14). These figures indicate that the margin of safety with IP administration of local anesthetics is small, so that potentially toxic doses should be avoided.

The peak central venous plasma concentrations measured in the present study are similar to those measured by Strömskag et al. (2) who reported peak plasma concentrations of 0.62 ± 0.25 μg/mL and 1.20 ± 0.44 μg/mL after single-dose administration of 20 mL of 0.25% and 0.5% bupivacaine, respectively. Peak times obtained in both studies were also similar; however, in a previous study (5) we measured considerably higher plasma concentrations after administration of a single dose of bupivacaine (21 mL of 0.5% bupivacaine with epinephrine 1:200,000). In

that study, measured mean peak plasma concentrations of bupivacaine were 2.07 ± 0.53 μg/mL in arterial plasma and 1.86 ± 0.45 μg/mL in central venous plasma compared with 1.47 ± 0.37 μg/mL in central venous plasma in the present study. A major difference in the design of both studies is that in the previous study, bupivacaine was administered in the operating room after completion of surgery but with the patients still under general anesthesia, whereas in both the present study and that of Strömskag et al. (2), injections were given during the recovery period. The results of the present study are therefore consistent with our previous suggestion that changes in cardiac output and local perfusion in patients experiencing pain may affect the absorption or disposition of local anesthetics, or both and therefore the plasma concentrations. In our opinion, injection of the local anesthetic during surgery is the method of choice because it will prevent rather than treat the onset of postoperative pain. Potentially toxic effects (in particular, on the central nervous system) of the resulting higher plasma concentrations will be negated by the (residual) effects of general anesthesia. However, these suggestions should be interpreted with caution and warrant further investigation.

Although in the present study infusions of bupivacaine were maintained for 24 h, plasma concentrations of bupivacaine did not reach a plateau. This is probably related to the observed increase in the degree of protein binding of bupivacaine. In human plasma, two classes of binding sites for bupivacaine can be distinguished: high-affinity, low-capacity sites on α_1-acid glycoprotein and low-affinity, high-capacity sites, mainly on albumin (25). In the concentration range encountered in this study, bupivacaine is mainly bound to α_1-acid glycoprotein. The observed increase in the protein binding of bupivacaine with time may therefore be attributed to the marked increase in the plasma concentration of this protein. Although the plasma concentration of albumin decreases with time, the fractional decrease is smaller than the fractional increase in the concentration of α_1-acid glycoprotein, and, consequently, the influence on the total degree of protein binding will be negligible.

In conclusion, this study shows that continuous IP infusion of bupivacaine provides adequate pain relief after cholecystectomy or lumbotomy. Although dermatomal spread of analgesia to pinprick is slightly higher after administration of a 0.5% bupivacaine solution, the administration of a 0.25% bupivacaine solution results in comparable clinical effects insofar as pain relief and restoration of pulmonary function are concerned. Given the lower plasma concentrations after administration of the 0.25% solution compared with the 0.5% solution, we recommend use of the more dilute solution.

We thank D. de Lange, MD, for assistance in evaluating the results; A. A. Vletter, BSc, and Mrs. M.P.R.R. Gladines, BSc, for assistance with the bupivacaine determinations and for determining the protein binding of bupivacaine; J. M. P. Serree, BSc, for determining the protein concentrations in plasma; and Mrs. J. I. Tieleman-Shamier for typing the manuscript. The cooperation of the staff of the Department of Surgery of the Sint Clara Hospital is greatly appreciated.

References

1. Scott NB, Mogensen T, Bigler D, Kehlet H. Comparison of the effects of continuous intrapleural vs epidural administration of 0.5% bupivacaine on pain, metabolic response and pulmonary function following cholecystectomy. Acta Anaesthesiol Scand 1989;33:535–9.
2. Strömskag KE, Reiestad F, Holmqvist ELO, Ogenstad S. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1988;67:430–4.
3. VadeBoncouer TR, Riegler FX, Gautt RS, Weinberg GL. A randomized, double-blind comparison of the effects of interpleural bupivacaine and saline on morphine requirements and pulmonary function after cholecystectomy. Anesthesiology 1989;71:339–43.
4. Frank ED, McKay W, Rocco A, Gallo JP. Interpleural bupivacaine for postoperative analgesia following cholecystectomy: a randomized prospective study. Reg Anesth 1990;15:26–30.
5. Van Kleef JW, Burm AGL, Vletter AA. Single-dose interpleural versus intercostal blockade: nerve block characteristics and plasma concentration profiles after administration of 0.5% bupivacaine with epinephrine. Anesth Analg 1990;70:484–8.
6. Veering BT, Burm AGL, Gladines MPRR, Spierdijk J. Age does not influence the serum protein binding of bupivacaine. Br J Clin Pharmacol 1991;32:501–3.
7. Burm AGL, van Kleef JW, de Boer AG. Gas chromatographic determination of bupivacaine in plasma using a support coated open tubular column and a nitrogen-selective detector. Anesthesiology 1982;57:527–9.
8. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. Br Med J (Clin Res) 1990;300:230–5.
9. Reiestad F, Strömskag KE. Interpleural catheter in the management of postoperative pain: a preliminary report. Reg Anesth 1986;11:89–91.
10. Camporesi EM. Intrapleural analgesia: a new technique (editorial). J Cardiothorac Anesth 1989;3:137–8.
11. Riegler FX, VadeBoncouer TR, Pelligrino DA. Interpleural anesthetics in the dog: differential somatic neural blockade. Anesthesiology 1989;71:744–50.
12. Blake DW, Donnan G, Novella J. Interpleural administration of bupivacaine after cholecystectomy: a comparison with intercostal nerve block. Anaesth Intensive Care 1989;17:269–74.
13. White PF. Patient controlled analgesia: an update on its use in the treatment of postoperative pain. Anesthesiol Clin North Am 1989;7:63–77.
14. Lee A, Boon D, Bagshaw P, Kempthorne P. A randomised double-blind study of interpleural analgesia after cholecystectomy. Anaesthesia 1990;46:1028–31.
15. Laurito CE, Kirz LI, Vadeboncouer TR, et al. Continuous infusion of interpleural bupivacaine maintains effective analgesia after cholecystectomy. Anesth Analg 1991;72:516–21.
16. Frenette L, Boudreault D, Guay J. Interpleural analgesia improves pulmonary function after cholecystectomy. Can J Anaesth 1990;38:71–4.
17. Brismar B, Pettersson N, Tokics L, Strandberg Å, Hedenstierna G. Postoperative analgesia with intrapleural administration of

bupivacaine-adrenaline. Acta Anaesthesiol Scand 1987;31:515–20.
18. Oxorn DC, Whatley GS. Post-cholecystectomy pulmonary function following interpleural bupivacaine and intramuscular pethidine. Anaesth Intensive Care 1989;17:440–3.
19. El-Baz N, Faber LP, Ivankovich AD. Intrapleural infusion of local anesthetic: a word of caution. Anesthesiology 1988;68: 809–10.
20. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–31.
21. Gin T, Chan K, Kan AF, Gregory MA, Wong YC, Oh TE. Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. Br J Anaesth 1990;64:662–6.
22. Seltzer JL, Larijani GE, Goldberg ME, Marr AT. Intrapleural bupivacaine—a kinetic and dynamic evaluation. Anesthesiology 1987;67:798–800.
23. Rademaker BMP, Sih IL, Kalkman CJ, et al. Effects of interpleurally administered bupivacaine 0.5% on opioid analgesic requirements and endocrine response during and after cholecystectomy: a randomized double-blind controlled study. Acta Anaesthesiol Scand 1991;35:108–12.
24. Rosenberg PH, Scheinin BM-A, Lepäntalo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 1987;67:811–3.
25. Denson D, Coyle D, Thompson G, Myers J. Alpha$_1$-acid glycoprotein and albumin in human serum bupivacaine binding. Clin Pharmacol Ther 1984;35:409–15.

REVIEW ARTICLE

Compartment Syndromes: Concepts and Perspectives for the Anesthesiologist

John T. Martin, MD

Department of Anesthesiology, Medical College of Ohio at Toledo, Toledo, Ohio

Background

Compartment syndromes have been discussed infrequently in literature familiar to anesthesiologists (1–4). Reports of compartment syndromes following vascular punctures in patients receiving anticoagulant therapy (5,6), plus recent allegations by plaintiffs that patient positioning can be a factor in causing postoperative compartment syndromes, establish a need to review the pathophysiology of compartmental ischemia and develop perspectives for the anesthesiologist.

Matsen (7) defined a compartment syndrome as a condition "in which the circulation and function of tissues within a closed space are compromised by increased pressure within that space." Dense osseofascial planes in extremities establish relatively unyielding boundaries that compartmentalize groups of muscles, nerves, and blood vessels. Blood flow through such a compartment can be disturbed by remote perfusion failure (vascular obstruction or systemic hypotension) or by increases in resistance to flow within the compartment itself (Table 1). Compartmental resistance may be increased by (a) an external application of pressure that decreases the effective size of the compartment and compresses its contents or (b) by an enlarged mass of compartment contents that crowds against rigid walls and elevates tissue pressure within the space. If compartmental ischemia is prolonged, it eventually initiates the sequence of events listed in Table 2. Neural dysfunction and muscle injury follow. Usually, prompt surgical decompression of the affected compartments is the only means of minimizing the functional impairment and structural damage of their contents.

Remote perfusion failure (Table 1) disrupts driving pressure whether due to systemic hypotension or some form of vascular obstruction distant from the affected compartments. Reperfusion, after the restoration of systemic pressure or the relief of obstruction, extravasates vascular contents through newly defective walls of the microcirculation, elevating compartment pressure. Perler and associates (8) believe that oxygen-derived free radicals, generated from xanthine oxidase during reperfusion, are the factors that damage the microvasculature. Patman (9) has reviewed compartment syndromes associated with peripheral vascular surgery.

Direct compartmental injuries are frequently associated with fractures, surgery, and multiple trauma. However, a wide range of other causes can elevate compartmental pressures (7) (Table 1). Tight dressings, tight surgical closure of fascial defects, or localized external pressure can decrease compartment size. Body parts, resting either against each other or upon a supporting object for protracted periods, may provide enough local external pressure to initiate the syndrome (10). Increases in the mass of compartment contents can result from elevated capillary pressure, low oncotic pressures, increased capillary permeability, trauma, bleeding, exercise of hypertrophic muscles, or infiltrated infusions.

In the presence of systemic normotension, Reneman (11) found that tissue pressures in normal compartments of the supine lower leg ranged from 9 to 15 mm Hg. In two instances of unilateral anterior compartment syndromes, one patient had a tissue pressure of 45 mm Hg in the hypertensive leg compartment and in the other patient the pathologic value was 67 mm Hg (11). Whitesides et al. (12) considered the normal mean arterial pressure in the microcirculation to be in the same range as systemic diastolic pressure and concluded that ischemia may begin at tissue pressures that are 10–30 mm Hg less than diastolic. Ashton (13) found that tissue circulation stopped when compressive compartmental pres-

Accepted for publication February 20, 1992.

Address correspondence to Dr. Martin, 4605 Woodland Lane, Sylvania, OH 43560.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

Table 1. Causes of Compartmental Ischemia

I. Remote Perfusion Failure
A. Vascular obstruction
B. Systemic hypotension
II. Increased Compartmental Resistance
A. Decrease in compartment size
1. Constriction by tight dressings or casts
2. Tight repair of surgical wounds
3. Local pressure
B. Increase in compartment volume
1. Bleeding and coagulopathies
2. Increased capillary permeability
a. Reperfusion edema (postischemic swelling)
b. Exercise (seizures and eclampsia)
c. Trauma and burns
d. Intraarterial drugs
3. Increased capillary pressure
a. Exercise
b. Venous obstruction
4. Decreased oncotic pressure
5. Infiltrated infusions
6. Muscle hypertrophy

Modified from Matsen FA. Clin Orthop 1975;113:8.

Table 2. Stages of Compartmental Ischemia

1. Hypoxic disruption of capillary boundaries
2. Escape of intravascular contents into adjacent tissues
3. Swelling (edema) of compartmental contents
4. Increasing compartmental pressure and perfusion impairment
5. Worsening ischemia and tissue necrosis
6. Myoglobinuria and renal damage
7. Severe fluid and electrolyte upsets
8. Local and systemic infection
9. Remote organ compromise or failure

sures reached 64 mm Hg in the forearm or 55 mm Hg in the calf. Systemic hypotension or arterial spasm reduced the magnitude of tissue pressure increases needed to impair perfusion. Elevation of a limb containing compartments with increased pressures can reduce arterial pressure sufficiently to arrest circulation in the affected compartments (14).

Total ischemia has been used experimentally to show that:

1. Neural abnormalities (paresthesias and hypesthesias) begin after about 30 min of ischemia and irreversible functional loss occurs if ischemia exceeds about 12 h (7,15,16)
2. Muscle changes begin after about 2 h, become irreversible after 4 h, and result in contractures after about 12 h (7,17)
3. Permeability of capillary endothelium increases after about 3 h of experimental total ischemia (7)
4. About 4 h of ischemia produces myoglobinuria that reaches its maximum after 3 h of reperfusion and may continue for 12 h (7,18).

Because partial perfusion exists in most clinical situations, the times required to produce changes in human tissue structure and function may be unpredictably longer than values quoted for total cessation of circulation in animals.

As the major dynamics of ischemia occur in affected tissues at the level of the microcirculation, pulses in peripheral vessels, as well as capillary refill in skin and nail beds, are frequently normal despite the clinical presence of a compartment syndrome in that extremity (7). When muscle necrosis is found at fasciotomy, its degree indicates grossly the extent and duration of ischemia. It may also correlate with the subsequent hardships of convalescence and the severity of residual dysfunction.

Compartment syndromes have been recognized in the shoulder, forearm, hand, buttocks, and lower leg. Physical signs depend on the structures involved and include sensory loss, muscle weakness, painful passive movement, and local tissue distention. Early decompression decreases postischemic swelling, tissue devitalization, and the likelihood of infection. Compartment pressure elevations lasting longer than 12 h have been associated with chronic functional defects, including sensory changes, motor weakness, and eventual contractures (19).

Vascular Punctures and Compartment Syndromes

Halpern et al. (5) have reported a compartment syndrome of the forearm that occurred after multiple attempts to obtain a blood sample for blood gas determination from a radial artery of a patient who had received chronic anticoagulant therapy. Neviaser and associates (6) described seven anticoagulated patients in whom brachial artery punctures for obtaining blood gas samples were followed by compartment syndromes in the forearm. Awareness that vascular punctures or cannulation can leak volume sufficient to elevate interstitial pressure (Table 1) and produce a compartment syndrome is essential when anesthetizing anticoagulated patients.

Irritating compounds, injected in or about vessels, have been associated with compartment syndromes. Bortolussi et al. (3) report an antecubital administration of diazepam that was followed by a compartment syndrome of the forearm. Surgical inspection of the brachial artery in the antecubital area showed no discernible puncture wound. Dry gangrene of the digits resulted despite surgical decompression. Doppler evidence of radial and ulnar arterial flow was present during the compartment syndrome.

Table 3. Traits of an "Axillary" Roll

1. *Thick and noncompressible enough* to raise the chest wall off of the surface of the operating table and free the down-side shoulder girdle from medial pressure
2. *Wide enough* to distribute its elevating pressure across the area of several ribs
3. *Long enough* to support the entire anteroposterior expanse of the down-side lateral chest wall
4. *Placed just caudad to the axilla* to avoid compression of axillary neurovascular contents

Patient Positioning and Compartment Syndromes

Upper Extremity

Shoulder. Nambisan and Karakousis (20) describe a young adult patient who remained in the left lateral decubitus position for 9 h during removal of a tumor from thoracic vertebrae. Toward the end of the procedure, the position was gradually converted to the semiprone, apparently without dorsal relocation of the down-side arm (21). When the patient was subsequently turned supine, the left (down-side) shoulder and adjacent neck were found to be extensively swollen. The left arm and hand were not involved, the quality of the radial pulse was good, and the patient could move the fingers. The blood pressure cuff had not been applied to the left arm and no attempts were made to use the left arm, subclavicular area, or neck for intravascular lines. By the following morning the swelling of the shoulder had become massive and the left arm and hand were immobile and numb. Emergency surgical decompression of the area was accomplished. Sensation and movement in the hand and forearm returned by the following day. Swelling of the shoulder subsided within several weeks and 1 yr later all functions of the shoulder, arm, and hand were again normal.

An "axillary" roll had been placed under the medial wall of the down-side axilla when the lateral position was established. Apparently the roll was either too thin to elevate the chest wall sufficiently to decompress the down-side shoulder or it had moved far enough cephalad in the axilla to have compressed axillary structures. Severe circumduction of the shoulder during the semiprone position may also have led to the ensuing compartment syndrome by compromising perfusion of the shoulder area.

Careful attention should be paid to the characteristics (Table 3) of the axillary roll when the lateral position is established. A stack of wrinkle-free folded towels or sheets usually suffices. Terry cloth bath towels should be avoided as supporting rolls because their rough surfaces may injure the skin at the points of contact. Reusable plastic lifts often become compressible and soon fail as supports.

When the lateral position is shifted to semiprone, the down-side arm should not be allowed to be seriously circumducted across the ventral chest wall lest its suprascapular nerve be stretched enough to produce postoperative shoulder pain (22). A convenient choice is to locate the down-side arm alongside, and slightly dorsal to, the semiprone trunk (21) with the radial pulse carefully checked for sufficiency after posture has been finalized.

Forearm. A century ago Richard von Volkmann recognized ischemic contractures of extremities after compression by excessively tight dressings (23). The entity was one of the earliest forms of what we now regard as a compartment syndrome.

On the volar surface of the dense interosseous membrane that connects the radius and ulna run the anterior interosseous nerve and its associated vessels. The anterior interosseous nerve, a terminal branch of the radial nerve lacking sensory fibers, provides motor supply to muscles of the forearm and hand. Direct injuries to forearms have produced compartment syndromes and dysfunction of anterior interosseous neurovascular bundles (24). A compartmentlike syndrome has been encountered in the forearm of a patient who had been supine during a general anesthetic. The tight binder retaining that supinated forearm on an arm board was alleged by the plaintiff to be compressive enough to initiate ischemia in the anterior interosseous compartment and cause an "anterior interosseous nerve syndrome." Weighed against the thousands of times each month that such a possibility exists in operating rooms in North America, the paucity of reports of such a complication strongly implies that the allegation in question was speculative and without merit. Nevertheless, such a possibility should be kept in mind as an arm is being well padded and retained on an arm board.

Lower Extremity

Exercise history. Intensive use of leg muscles may increase pressures within compartments of the leg to the point of compromising circulation and producing pain. In the acute form, the process leads to ischemic destruction of compartment contents. In the chronic syndrome, exertional pain is relieved by rest and recurs with additional exercise (25). The underlying cause is likely to be hypertrophic musculature within a compartment rather than a poor vascular supply to that compartment. Therefore, a history of recurrent lower leg pain with exercise should alert the anesthesiologist to the possibility of abnormal perfusion of

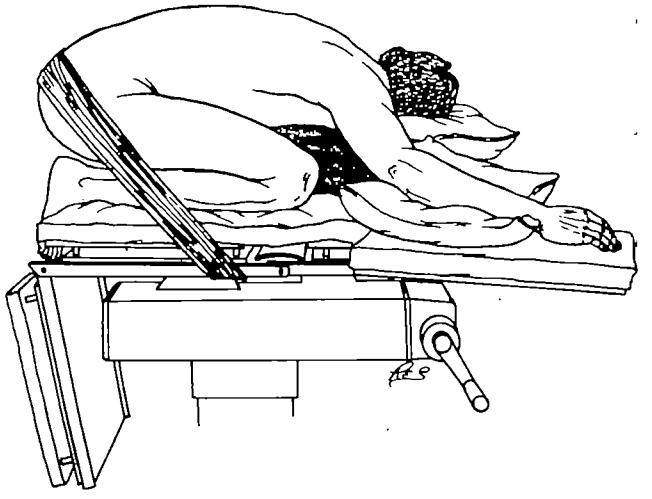


Figure 1. The tuck position. Severe flexion of knees and hips can angulate vessels and produce ischemia of the extremities. (Redrawn with permission from Wayne SJ. The tuck position for lumbar disc surgery. J Bone Joint Surg 1967;49:1195. Dr. Wayne currently uses only a modified tuck position as reported in Wayne SJ. A modification of the tuck position for lumbar spine surgery. Clin Orthop 1984;184:212.)

the limb and the potential for development of a compartment syndrome in the presence of sustained hypotension or extended external pressure on the leg during a surgical procedure.

Prone position. Many variations of the prone position have been recommended as methods of avoiding pressure on the abdomen that would congest perispinal vasculature and compromise hemostasis during lumbar area surgery (26,27). Any prone position that requires ventroflexion of the lumbar spine to separate the spinous processes and widen the dorsal aspects of the intervertebral spaces renders the lower extremities dependent and susceptible to pooling of significant amounts of blood. The remedy has been to apply compressive wrappings from foot to midthigh bilaterally before pronating the patient. If tight enough, the wraps fit the description of compressive bandages that decrease compartment size (Table 1). The fact that gravity aids arterial flow into the dependent wrapped areas probably preserves perfusion and accounts for the scarcity of reports of compartmental syndromes after leg wrapping. I am aware, however, of several conversational anecdotes describing wrapped legs that became ischemic after pronation. Care should be taken to see that the tension applied to the wrappings is not excessive and that the proximal limit of the wrap does not act as a tourniquet.

An extreme degree of flexion of the knees and hips (Figure 1) was a component of an early kneeling variety of the prone position variously known as the "carpenter's rule position," the "Muhammedan praying position," or the "tuck position." Reports of postoperative myoglobinemia leading to renal failure began to appear after fairly widespread use of the position (28,29). Although not specified at the time, vascular obstruction in the severely angulated inguinal and/or popliteal regions undoubtedly produced remote perfusion failure and resulted in compartment syndromes in the lower extremities. Apparently the position is no longer extensively used.

Recently, Aschoff and associates (30) reported two instances of compartment syndromes after lumbar disk surgery with the patients in a "genu-pectoral" (knee-chest) position with a pad between the Achilles tendon and buttocks. The result is undoubtedly much tighter flexion of legs on thighs than used in the kneeling position on an Andrews Frame. The ability of their pad to compress calves was not described. One patient was in position for slightly more than 3 h, the other for 4 h. In each case 12 uneventful postoperative hours were followed by the development of compartment syndromes.

Lithotomy position. Instances of compartment syndromes have been reported to follow use of several versions of the lithotomy position, with emphasis being on the considerable length of time that the patient remained in the position (31–33). Each of the several different leg holders available presents both assets and problems (Figures 2 and 3). Most can compress extremity tissue to some degree and all can be elevated enough to create a potentially damaging perfusion gradient. The term "stirrup" should be abandoned because its careless jargonistic use has rendered it nondescriptive.

Perhaps the least complicated holder is either a cloth sling that encircles the instep and heel (Figure 2A) or a cloth boot that encases the foot. It does not compress extremity tissue, but the knee area is not stabilized against medial and lateral pressures.

A "knee crutch" (Figure 2B) consists of an angulated metal trough that supports the popliteal fossa and extends a short distance cephalad on the dorsal thigh and caudad on the calf. The entire foot and the portion of the leg that is beyond the distal edge of the device are unsupported. Consequently, the weight of the foot and lower leg can produce a leverlike action that compresses the calf against the distal edge of the holder. Its ability to compress the calf and popliteal fossa makes the knee crutch a questionable choice as a support for lengthy procedures done in the lithotomy position. Recently, a trial (34) involved bilateral lower extremity compartment syndromes that followed a 10-h gynecologic procedure done with the

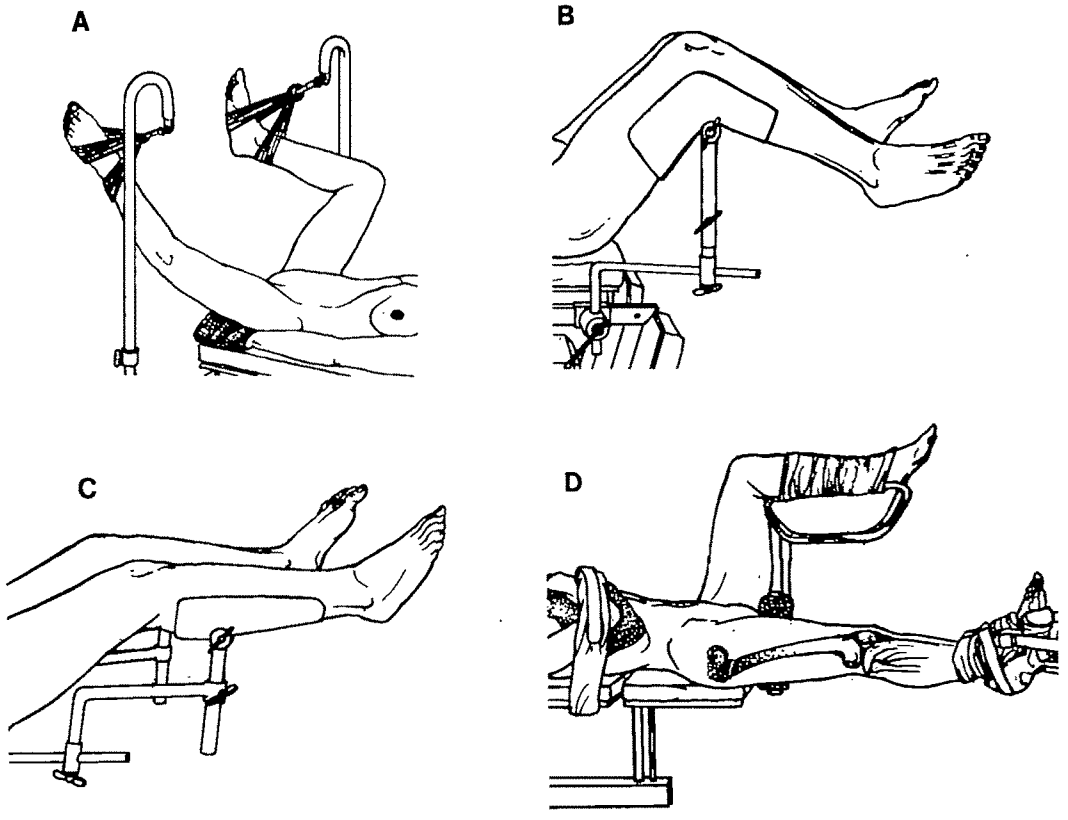


Figure 2. Varieties of lithotomy leg holders (protective padding omitted for clarity). **A.** Cloth slings attached to vertical "shepherd's crook" or "candy cane." (Cloth bootie may replace slings.) **B.** Knee crutch ("Bierhoff" leg holder). **C.** Calf rest. **D.** Calf rest for elevated limb while injured extremity is in surgical traction. [Figures modified with permission from Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987: (A) from Figure 8-1 on page 58, (B) from Figure 7-2 on page 54, (C) from Figure 12-4 on page 120, and (D) from Figure 18-4 on page 227.]

patient in this type of leg holder. Now under litigation from the same institution is a similar problem that was previously reported by Adler and associates (33). Leff and Shapiro (35) warned against use of the knee crutch leg holder in extended procedures.

In the device depicted in Figure 2C, the calf rests in a semicylindrical trough and bears the complete weight of the lower extremity. The unit is used often for prolonged low lithotomy positioning. It is not free of the potential for significant compression of the calf if the extremity is heavy or if the contained limb is used as an arm rest by a standing member of the surgical team.

A variant of this arrangement supports the elevated limb of a patient in the hemilithotomy position on a fracture table (Figure 2D). Two patients developed compartment syndromes in the elevated limb after being in the hemilithotomy position for intramedullary nailing of the femur for 5.5 and 6.0 h, respectively (36).

A foot holder resembles the plantar and dorsal halves of a ski boot with its proximal end flared somewhat (Figure 3A). With this device the weight of the extremity is borne by the holding boot, which needs careful padding between its interior and the heel and sole of the patient's foot. Despite the firmly held limb, no pressure is placed on the popliteal fossa and almost none is placed against the distal calf. This unit obviously requires an intact skeleton in the contained extremity.

A popular device combines the knee crutch (Figure 2B) and the foot holder (Figure 3A) above by using a telescoping rod to connect the knee crutch and the foot holder (Figures 3B, C). It allows good distribution of the weight of the extremity in the holder as well as suitable adjustments of its components to fit the dimensions of the patient. Nevertheless, the device still does not obviate the potential for compression of the popliteal fossa and upper calf by the weight of the supported limb. It may be the holder of choice for the exaggerated lithotomy position (Figure 3C), as its firm support of the elevated extremities stabilizes the position of the symphysis pubis for perineal access to retropubic structures.

A modification of a fabric-covered arm frame has provided a soft sling to support most of the lower leg. The proximal end of the frame is widened somewhat and the unit is usually encased in a tubular "stock-

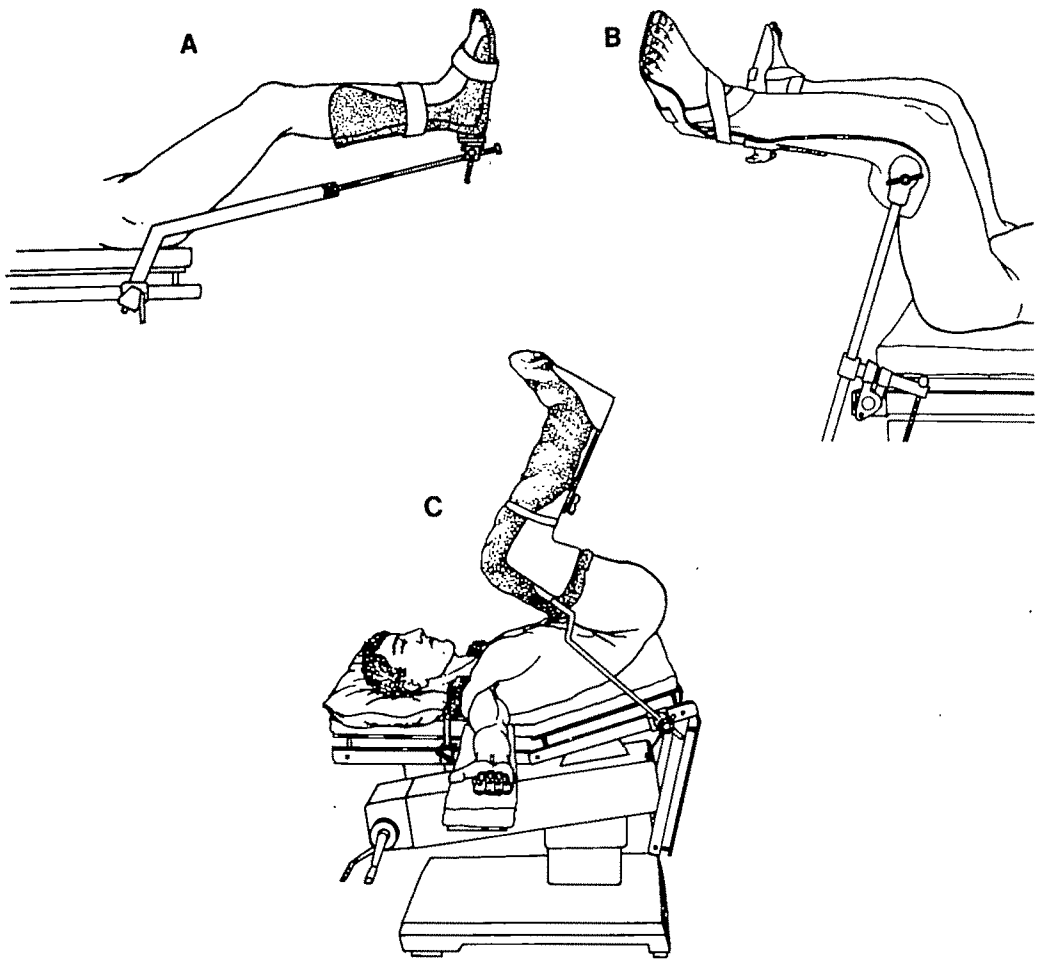


Figure 3. Varieties of lithotomy leg holders (continued) (protective padding omitted for clarity). **A.** Semiboot foot holder that frees popliteal fossa and bulk of calf from pressure. **B.** Knee-crutch-and-boot, distributing weight of extremity between popliteal fossa, calf, and foot. **C.** Knee-crutch-and-boot in exaggerated lithotomy position to firmly retain leg and stabilize tilted pelvis. (Figures modified with permission from: (A) Illustration of item 10001 in brochure of Allen Medical Systems, Bedford Heights, Ohio; (B) Figure 6-4 in Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:45; (C) Figure 7-3 in Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:55.)

inette." It distributes the weight of the extremity over the posterolateral surface of the abducted and externally rotated limb (37).

Recently, an elderly gentleman, who had a stenotic carotid artery, intermittent claudication, hypertension on medication, and an old history of a coronary artery bypass procedure that was followed by an angioplasty of a lower extremity, developed a pelvic tumor that needed an extensive abdominopelvic resection. All of the monitors required to control his cardiovascular status during and after the operation were placed before an uncomplicated induction of combined general and epidural anesthesia. His legs were wrapped with compressive dressings to "prevent pooling of blood," then further wrapped into padded leg holders (probably the type shown in Figure 3C) for the low lithotomy position, and the table was tilted about 15° head down. The difficult surgical procedure lasted approximately 10 h. Hypotension that followed the induction of anesthesia was allowed to continue during the first 4 h to minimize surgical bleeding. Otherwise, the monitoring and management of the anesthetic was thoughtful and excellent. Twelve hours after anesthesia, compartment syndromes were recognized in both lower extremities. Fasciotomies were performed and subsequently needed revision. Muscle necrosis was extensive. After a stormy, septic 5-mo postoperative course that included renal and pulmonary failure, he suffered a sudden cardiac arrest from which he could not be resuscitated.

By retrospective calculation, the final operative position placed his feet about 20 in. above the level of his heart (Figure 4). In the presence of systemic arteriosclerosis and treated hypertension, the driving pressure needed to perfuse sclerotic vessels in his

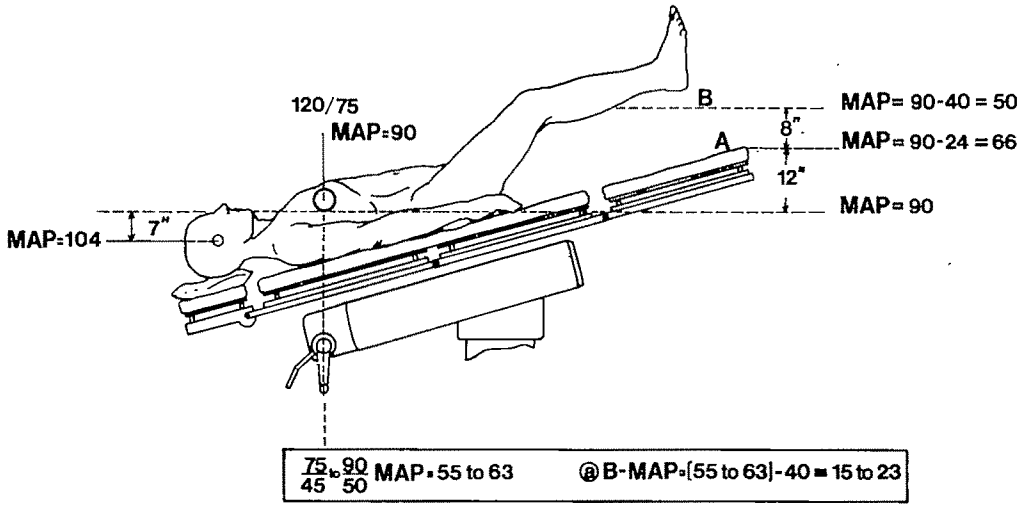


Figure 4. Calculated effects of gravity on perfusion pressure in elevated lower extremities. Pressures vary 2 mm Hg per vertical inch (2.5 cm) (38). (Mean arterial pressure [MAP] estimated as 0.33 [SBP − DBP] + DBP, where SBP = systolic blood pressure and DBP = diastolic blood pressure.) Rectangle displays effects of systemic hypotension on calculated perfusion pressure in distal calves. Sclerotic vessels and external pressures from leg rests or leg wrappings would increase the ischemic potential. (Note: the elevated single leg in the hemilithotomy position [Figure 2D] would be about 18–20 in. above heart level with MAP at the calf being approximately 36–40 mm Hg less than cardiac MAP.)

legs was increased by (a) compressive leg bandages, (b) the uphill gradient to his legs in low lithotomy, (c) additional wrappings to secure his legs in the holders, and (d) adding head-down tilt to the lithotomy position. During the hypotensive period, mean arterial blood pressure (MAP) at the heart ranged between 55 and 63 mm Hg. Simultaneously, because MAP varies 2 mm per vertical inch (38), the MAP in the elevated, wrapped calves (Figure 4) would have hovered around 20 mm Hg in structures accustomed to the chronically high MAP of hypertension. Vasodilation from epidural anesthesia was probably not a useful factor in aiding leg perfusion because of the simultaneous presence of external compression from the leg wrappings. A significant issue was the 10 or more hours of lithotomy position. Extensive myonecrosis at fasciotomy indicated that the perfusion deficit in affected compartments had been severe and lengthy.

Varying opinions exist about the ability of postoperative analgesia to impede recognition of a compartment syndrome. Based on evidence that was open to serious question and involved only one patient, Strecker and associates (39) asserted that a continuous infusion of epidural bupivacaine for postoperative analgesia masked the development of compartment syndrome pain in a leg from which a donor bone graft had been taken. While that syndrome was induced by invasive surgery and not by patient posture, their implication indicted epidural analgesia in all compartment syndromes. Recently, by contrast, Montgomery and Ready (4) reported two patients in whom, after use of the lithotomy position for prolonged genitourinary procedures under combined general anesthesia and epidural lidocaine, unilateral compartment syndromes requiring fasciotomies were "readily diagnosed" despite the presence of otherwise effective postoperative epidural morphine analgesia accomplished by intermittent injection of functioning catheters. Reinjecting the catheters did not relieve the development of excessive limb pain in either of their patients, suggesting a sympathetic perivascular pathway for the pain. When the potential for a compartment syndrome exists, they recommend a high index of suspicion plus vigilant clinical evaluation to detect its onset and institute treatment. Additional experience is needed to resolve the controversy, but data holding epidural analgesia responsible for obscuring the diagnosis of a compartment syndrome are sparse and the evidence is flimsy at best.

Perspectives

Because the entity of compartment syndromes still may be unfamiliar to some practitioners who require use of the lithotomy position (32), the anesthesiologist should bear in mind the following considerations:

1. The duration of lithotomy position is apparently a matter of concern. Compartment syndromes have been associated with several different types of leg holders when lithotomy position time has ex-

ceeded about 5 h (31–34). Long procedures that require lithotomy for only a part of the operation can often be planned so that either much of the procedure can take place before establishment of lithotomy or the patient's position can be changed to an alternative posture for the balance of the operation when lithotomy is no longer needed.

2. For a prolonged procedure, a leg support that allows pressure either in the popliteal fossa or on the calf should be avoided despite seemingly adequate padding. An exception is the necessary use of present models of fracture tables with the hemilithotomy position; however, the table manufacturers should be asked to make design modifications in the holder for the elevated leg so that the calf is freed from compression.

   Use of the popliteal support, or knee crutch, which allows the lever action of an unsupported foot to intensify the pressure of the distal lip of the crutch on the patient's calf, should be limited to brief procedures and the crutch must always be very carefully padded.
3. Throughout the procedure, blood pressure should be maintained carefully within ranges that are normal for that patient. Loss of driving pressure for blood flow in elevated extremities allows compartmental ischemia to occur at lesser levels of increased compartment pressure. Hypotension used to conserve blood loss and replacement in the multiple-trauma patient may intensify existing vascular injuries in extremities. The risks posed by vasoconstrictor drugs that increase peripheral resistance and decrease compartment blood flow should be borne in mind. Of major importance are the warnings of Matsen (7) and Ashton (13) that, once a compartment syndrome has been diagnosed, elevating the involved extremity in an attempt to promote venous drainage only lowers driving pressure into that limb and further diminishes perfusion of its tight compartments.
4. Wrapping elevated legs to prevent blood from pooling therein is thoughtless and counterproductive.
5. Detecting the onset of compartment syndromes during anesthesia is apt to be impossible. Distal pulses in an extremity, as well as capillary refill in the ipsilateral nail beds, remain essentially unchanged despite the development of the syndrome. Reperfusion is needed to produce the tissue edema that initiates a compartment syndrome; usually this adds a time factor to the development of the syndrome that may extend its earliest recognition to well beyond the termination of anesthesia. Thus, measuring compartmental tissue pressures during anesthesia and surgery may be neither practical nor informative. More prompt indicators of an incipient compartment syndrome should be sought as experience accumulates.
6. The choice of anesthesia for lengthy procedures to be done in the lithotomy position has little bearing on the potential for diagnosis of a compartment syndrome at or after the end of the case. Recent evidence (4) indicates that postoperative epidural analgesia did not prevent early recognition of the development of the syndrome.

Data about the association of compartment syndromes with vascular punctures and patient positioning are sparse, anecdotal, and not susceptible to statistical analysis. However, published reports and recent litigation confirm distinct hazards reliably enough to compel attention. Although compartment syndromes associated with anesthesiologic maneuvers are admirably infrequent, they do occur. The uncomfortable conclusion is that some may be preventable. Familiarity with the circumstances that encourage development of a compartment syndrome will allow the anesthesiologist to cooperate effectively with other members of the surgical team in avoiding this distressing cause of major postoperative morbidity.

References

1. Lydon JC, Spielman FJ. Bilateral compartment syndrome following prolonged surgery in the lithotomy position. Anesthesiology 1984;60:236–8.
2. Goldstein PJ. The lithotomy position: surgical aspects: obstetrics and gynecology. In: Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:49–50.
3. Bortolussi ME, Hunter JG, Handal AG. Forearm compartment syndrome after diazepam administration. Anesthesiology 1991;75:159–60.
4. Montgomery CJ, Ready LB. Epidural opioid analgesia does not obscure diagnosis of compartment syndrome resulting from prolonged lithotomy position. Anesthesiology 1991;75:541–3.
5. Halpern AA, Mochizuki R, Long CE III. Compartment syndrome of the forearm following radial artery puncture in a patient treated with anticoagulants. J Bone Joint Surg (Am) 1978;60:1136–7.
6. Neviaser RJ, Adams JP, May GI. Complications of arterial puncture in anticoagulated patients. J Bone Joint Surg (Am) 1976;58:218–20.
7. Matsen FA. Compartmental syndrome: a unified concept. Clin Orthop 1975;113:8–14.
8. Perler BA, Tomeh AG, Bulkley GB. Inhibition of the compartment syndrome by the ablation of free radical-mediated reperfusion injury. Surgery 1990;108:40–7.
9. Patman RD. Compartmental syndromes in peripheral vascular surgery. Clin Orthop 1975;113:103–10.
10. Owen CA, Murabek SJ, Hargens AR, et al. Intramuscular pressures with limb compression. Clarification of the pathogenesis of the drug-induced muscle compartment syndrome. N Engl J Med 1979;300:1169–72.
11. Reneman RS. The anterior and the lateral compartment syndrome of the leg. Paris: Mouton, 1968.
12. Whitesides TE, Haney TC, Morimoto K, Harada H. Tissue

pressure measurements as a determinant for the need for fasciotomy. Clin Orthop 1975;113:43–51.
13. Ashton H. Critical closing pressure in human peripheral vascular beds. Clin Sci 1962;22:79–87.
14. Ashton H. Effect of inflatable plastic splints on blood flow. Br Med J 1966;2:1427–30.
15. Malan E, Tattoni G. Physio- and anatomo-pathology of acute ischemia of extremities. J Cardiovasc Surg 1963;17:212–25.
16. Parkes AR. Traumatic ischaemia of peripheral nerves with some observations on Volkmann's ischemic contracture. Br J Surg 1944;32:403–12.
17. Whitesides TE Jr, Hirada H, Morimoto K. The response of skeletal muscle to temporary ischemia: an experimental study. J Bone Joint Surg (Am) 1971;53:1027–8.
18. Montagnani CA, Simeone FA. Observations on the liberation and elimination of myohemoglobin and hemoglobin after release of muscle ischemia. Surgery 1953;34:169–84.
19. Matsen FA, Clawson DK. The deep posterior compartmental syndrome of the leg. J Bone Joint Surg (Am) 1975;57:34–9.
20. Nambisan RN, Karakousis CP. Axillary compression syndrome with neurapraxia due to operative positioning. Surgery 1989;105:449–54.
21. Singh I. The prone position: surgical aspects. In: Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:187 (and Figure 16-7).
22. Schweiss JF, quoted in Lawson NW. The lateral decubitus position: anesthesiologic considerations. In: Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:175–6.
23. Volkmann R. Die ischaemischen muskellamungen und kontraktunen. Zbl Chir 1881;51:801–11.
24. Hill NA, Howard FM, Huffer BR. The incomplete anterior interosseous nerve syndrome. J Hand Surg (Am) 1985;10:4–7.
25. Reneman RS. The anterior and the lateral compartmental syndrome of the leg due to intensive use of muscles. Clin Orthop 1975;113:69–80.
26. Singh I. The prone position: surgical aspects. In: Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:181.
27. Martin JT. The prone position: anesthesiologic aspects. In: Martin JT, ed. Positioning in anesthesia and surgery. 2nd ed. Philadelphia: WB Saunders, 1987:191.
28. Gordon BS, Newman W. Lower nephron syndrome following prolonged knee-chest position. J Bone Joint Surg (Am) 1953; 35:764–8.
29. Keim HA, Weinstein JD. Acute renal failure—a complication of spine fusion in the tuck position. J Bone Joint Surg (Am) 1970;52:1248–50.
30. Aschoff A, Steiner-Milz H, Steiner H-H. Lower limb compartment syndrome following lumbar discectomy in the knee-chest position. Neurosurg Rev 1990;13:155–9.
31. Reddy PK, Kaye KW. Deep posterior compartmental syndrome: a serious complication of the lithotomy position. J Urol 1984;132:144–5.
32. Khalil IM. Bilateral compartmental syndrome after prolonged surgery in the lithotomy position. J Vasc Surg 1987;5:879–81.
33. Adler LM, Loughlin JS, Morin CJ, Haning RV. Bilateral compartment syndrome after a long gynecologic operation in the lithotomy position. Am J Obstet Gynecol 1990;162:1271–2.
34. Allen v. Granai et al. United States District Court, District of Rhode Island.
35. Leff RG, Shapiro SR. Lower extremity complications of the lithotomy position: prevention and management. J Urol 1979; 122:138–9.
36. Dugdale TW, Schutzer SF, Deafenbaugh MK, Bartosh RA. Compartment syndrome complicating use of the hemilithotomy position during femoral nailing. J Bone Joint Surg (Am) 1989;71:1556–7.
37. Reddy PK, Ami Sidi A, Lange PH. Modified stirrups for dorsal lithotomy positioning. Urol Clin North Am 1990;17:131–3.
38. Enderby GEH. Postural ischemia and blood pressure. Lancet 1954;1:185–7.
39. Strecker WB, Wood MB, Bieber EJ. Compartment syndrome masked by epidural anesthesia for postoperative pain. J Bone Joint Surg (Am) 1986;68:1447–8.

Seizures Occurring in Pediatric Patients Receiving Continuous Infusion of Bupivacaine

Rita Agarwal, MD, David P. Gutlove, MD, and Charles H. Lockhart, MD

Department of Anesthesiology, The Children's Hospital, Denver, Colorado

Continuous infusion of local anesthetics through regional techniques has recently gained popularity for the treatment of postoperative pain; however, information on the appropriate safe and effective doses and infusion rates for use in children is still limited. The following two case reports illustrate bupivacaine toxicity manifested by seizures in the absence of cardiovascular problems caused by the cumulative effect of a continuous infusion. Although different sites (intrapleural in case 1 and epidural in case 2) were used, the blood levels at the time of the seizures are remarkably similar.

Case 1

A 3-yr-old, 9.4-kg girl with a history of chronic interstitial lung disease was scheduled for a diagnostic right middle lobe lung biopsy. Preoperatively, her physical examination was significant for mild respiratory distress with peripheral clubbing, cyanosis, and diffuse telangiectatic skin lesions. While breathing 2 L/min oxygen via nasal cannula, oxygen saturation was 95%. The $Paco_2$ was normal, and she had no history of carbon dioxide retention. Chest radiograph demonstrated a chronic interstitial pulmonary process.

In the operating room, room air oxygen saturation was measured at 88%. The procedure was performed during general anesthesia with oxygen, nitrous oxide, and isoflurane. Before closure of the thoracotomy, the surgeon placed an intrapleural catheter under direct vision, positioning it posteriorly from the incision site. The internal end was loosely sutured in place to prevent migration of the catheter tip. The trachea was extubated in the operating room, and she was then taken to the postanesthesia care unit, where she was given oxygen by face shield and her heart rate, respiratory rate, arterial blood pressure, and oxygen saturation were monitored. She received 2.5 mL of 0.25% bupivacaine (0.66 mg/kg) with 1:200,000 epinephrine via the intrapleural catheter with good pain relief within 10 min. She did not experience any cardiovascular or neurologic changes.

A continuous infusion of 0.25% bupivacaine without epinephrine at a rate of 0.1 $mL \cdot kg^{-1} \cdot h^{-1}$ (0.25 $mg \cdot kg^{-1} \cdot h^{-1}$) was started in the intensive care unit 1 h after the initial bolus dose. Five hours later, the infusion rate was increased to 0.2 $mL \cdot kg^{-1} \cdot h^{-1}$ (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) after the patient complained of pain localized to the incision site. The infusion remained at this rate for the next 16 h. She was closely monitored during this time and noted by the nurses to be very calm, quiet, easy to care for, and apparently pain free. Twenty-one hours after the start of the infusion, she had two tonic-clonic seizures, each lasting 20–40 s within 3–4 min of each other. Each seizure was followed by increased lethargy. Her vital signs, including respiratory rate and oxygen saturation, remained stable throughout these events, and there was no evidence of hypoxia or postictal apnea. There were no changes in her electrocardiogram before or after her seizures. The infusion was promptly discontinued and the intrapleural catheter removed. The patient received 100 mg of phenobarbital intravenously and had no further recurrence of seizures. Blood samples sent for analysis of electrolytes, calcium, magnesium, glucose, and bupivacaine concentration were normal except for a bupivacaine level of 5.6 $\mu g/mL$.

The lung biopsy revealed evidence of multiple angiomas and arteriovenous malformations. The remainder of her hospital course was uneventful.

Case 2

This patient was a 9-yr-old, 26-kg girl with a history of cerebral palsy after premature birth at 28 wk, scheduled for a selective dorsal rhizotomy. Her

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Defense or other departments of the United States Government.

Accepted for publication December 26, 1991.

Address correspondence to Dr. Lockhart, Department of Anesthesiology, The Children's Hospital, 1056 East 19th Avenue, Denver, CO 80218.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

symptoms at the time of surgery consisted of profound spasticity of the lower extremities that prevented ambulation. She was of normal intelligence and had no other medical problems.

An uneventful anesthetic was induced and maintained with oxygen, nitrous oxide, and halothane by inhalation. An epidural catheter was introduced via the caudal route, then advanced without difficulty to approximately the L-1 area. During the surgical procedure, on exposure of the dura, the surgeon identified and confirmed the position of the catheter at L-1. After an 11-h procedure, the patient's endotracheal tube was removed in the operating room, and she was taken to the postanesthesia care unit. Her initial complaint of pain was treated with 0.5 mL/kg of 0.25% (1.25 mg/kg) bupivacaine with 1:200,000 epinephrine. There was no evidence of intravascular or intrathecal injection. A continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine was initiated at the rate of 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ (1.25 $mg \cdot kg^{-1} \cdot h^{-1}$). She was monitored in the intensive care unit for the first 24 h, then transferred to the ward where her electrocardiogram was continuously monitored. Other vital signs (respiratory rate, blood pressure) were checked every 4 h. On the third postoperative day, 56 h after the start of the infusion, the patient had a total of three tonic-clonic seizures, each lasting <30 s. As with the previous case, her blood pressure, respiratory rate, heart rate, and electrocardiogram remained stable throughout, and she had no evidence of postictal apnea. The patient had reported a "falling" or "tumbling" sensation several hours before the seizures but had otherwise been noted by the nurses to be exceptionally calm and free of complaints preceding the onset of the seizures. The infusion was stopped immediately after the first seizure. The second seizure occurred 2 h later and was treated by half a loading dose of phenobarbital. The third seizure occurred 30 min after the second and was treated by completing the loading dose of phenobarbital. A blood sample drawn after the first seizure was analyzed for multiple variables and was normal except for a bupivacaine level of 5.4 μg/mL. She had no further seizures, and the rest of her hospital course was uneventful.

Discussion

Continuous infusions of bupivacaine by both the intrapleural and epidural routes have been shown to be safe and effective for managing postoperative pain in pediatric patients (1,2). Systemic toxicity from bupivacaine infusions with associated venous concentrations has not been previously reported in children.

The plasma level of bupivacaine associated with central nervous system toxicity in adults has been estimated to be 4 μg/mL (3); however, Scott (4) suggests that the absolute toxic plasma concentration may be more dependent on the rate of increase than on any exact concentration, with the higher absolute levels tolerated when the rate of increase is slow. McIlvaine et al. (1) reported several patients with levels >4 μg/mL and one child with a plasma bupivacaine level >7 μg/mL who had no evidence of central nervous system toxicity. However, some of these patients had received diazepam in the first 24 postoperative hours, which may have masked central nervous system toxicity.

Patients receiving infusions of bupivacaine may be at an increased risk for developing systemic toxicity because of the pharmacokinetics of bupivacaine. Burm et al. (5) used a stable isotope method to investigate the pharmacokinetics of lidocaine and bupivacaine after epidural and subarachnoid administration in healthy adults. They showed that both local anesthetics underwent biphasic absorption, regardless of route of administration. The initial absorption rates for lidocaine and bupivacaine were similar; however, the slow absorption phase was much longer for bupivacaine. This would seem to indicate that there is a potential for accumulation of bupivacaine in plasma during prolonged infusion. Desparmet and colleagues (2) in a study of six children receiving continuous epidural infusions of 0.25% at a rate of 0.08 $mL \cdot kg^{-1} \cdot h^{-1}$ (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) for 48 h found that there was no significant increase in the plasma levels during the course of the infusion. Plasma levels ranged between 0.2 and 1.2 μg/mL; however, there was considerable interpatient variability. McIlvaine and associates (1), on the other hand, did find evidence of accumulation in patients treated with intrapleural infusion of 0.5–1.0 $mL \cdot kg^{-1} \cdot h^{-1}$ of 0.25% bupivacaine for 24 h.

Recommendations for dose limits may be implied from the work of Desparmet et al. (2) and McIlvaine et al. (1). The latter used, and recommended, a higher limit of 0.5–1 $mL \cdot kg^{-1} \cdot h^{-1}$ of 0.25% bupivacaine with 1:200,000 epinephrine (1.25–2.5 $mg \cdot kg^{-1} \cdot h^{-1}$). Although none of their patients showed signs of systemic toxicity, the plasma bupivacaine concentrations exceeded the recommended peak concentrations for adults (whether this peak concentration is different in children is unknown). They suggest an infusion rate not to exceed 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ (1.25 $mg \cdot kg^{-1} \cdot h^{-1}$) 0.25% bupivacaine. Neither of the patients in these case reports was receiving infusion rates in excess of that suggested by McIlvaine et al. (1). The first patient's lung biopsy revealed the presence of multiple angiomas and arteriovenous malformations that may have contributed to increased systemic absorp-

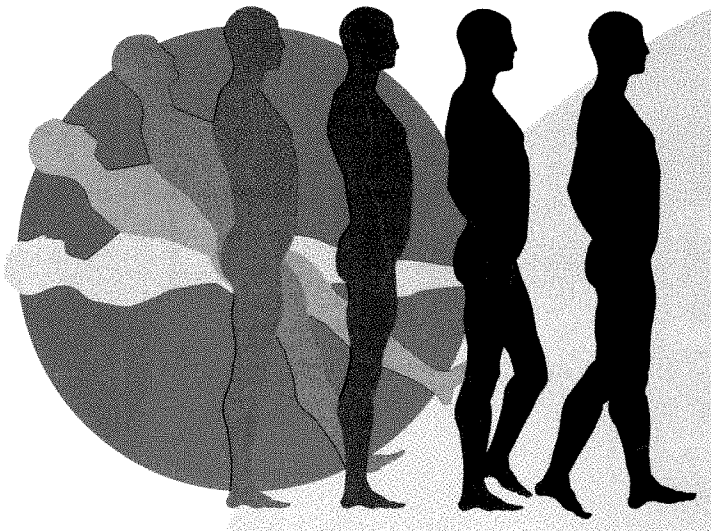
tion. The second patient had had her dura incised and repaired, which could have altered the rate of systemic absorption. The similar blood levels of 5.4 and 5.6 μg/mL were measured at the onset of the seizure activity.

These patients' prodromal warning signs are conspicuous for the absence of those usually described with acute toxicity (such as numbness of legs and tongue, tinnitus, nystagmus, dysphoria, lightheadedness, shivering, muscular twitching, feelings of impending doom or death). Perhaps the most notable observations are that while not appearing markedly obtunded, the patients were quiet, restful, and did not initiate spontaneous communication. It is therefore important to talk to the verbal child frequently to elicit these early premonitory signs. Fortunately, there was no evidence of cardiovascular instability—no dysrhythmia or hypotension, as has commonly been described accompanying central nervous system toxicity with bupivacaine.

In summary, two cases of bupivacaine toxicity during extended continuous infusions are described. Improved communication with the patients may have allowed earlier detection of toxicity. These cases demonstrate the need for further prospective critical evaluation of the proper dosage for effective and safe postoperative pain control using infusion of local anesthetics by various routes.

References

1. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988; 69:261–4.
2. Desparmet J, Meistelman C, Barre J, Saint-Maurice C. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. Anesthesiology 1987;67:108–10.
3. Tucker GT. Pharmacokinetics of local anesthetics. Br J Anaesth 1986;58:717–31.
4. Scott DB. Evaluation of clinical tolerance of local anesthetic agents. Br J Anaesth 1975;47:328–33.
5. Burm AGL, van Kleef JW, Vermeulen NPE, Breimer DD, Spierdij KJ. Absorption kinetics of lidocaine and bupivacaine following epidural and subarachnoid administration: a study using a stable isotope method (abstract). Anesthesiology 1986; 65:A206.



"The duration of action of mivacurium defines a new class of non-depolarizing neuromuscular blocking drugs."p.397

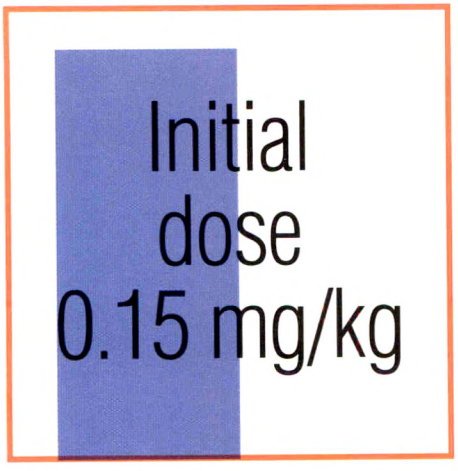
Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth.* 1989;63:393-399.

Please see full prescribing information for **M**IVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

New MIVACRON®

The first and only short

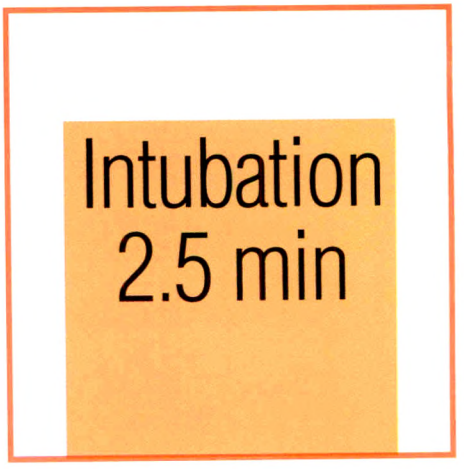
Duration of action and spontaneous recovery profile approximately one-third to one-half that of intermediate agents such as atracurium or vecuronium



Profound neuromuscular block

Recommended initial adult dose

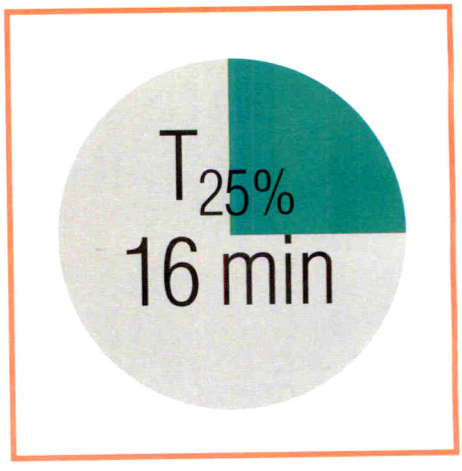
The recommended initial adult bolus dose of 0.15 mg/kg (administered over 5 to 15 seconds) provides profound neuromuscular block.



Generally good to excellent intubating conditions

Useful for routine intubation

MIVACRON provides generally good to excellent intubating conditions in 2.5 minutes at a dose of 0.15 mg/kg. Succinylcholine remains the drug of choice for rapid sequence intubation.



Short duration of action

Well-suited for short procedures

Duration of clinically effective block (time to 25% recovery of T_1) following injection of 0.15 mg/kg is 16 minutes, making **M**IVACRON excellent for short procedures.[1]

from Burroughs Wellcome Co.

acting nondepolarizer

Reduce spontaneous recovery time by up to 50% *vs* vecuronium

	Duration of continuous infusion (min)	Recovery times (min) Off-25%*	25-75%	5-95%
MIVACRON (n=25)	**86.2±5.6**	**5.7±0.3**	**6.4±0.2**	**13.6±0.6**
ecuronium n=18)	96.8±6.6	12.7±1.3†	13.8±0.9‡	32.0±1.2‡§
tracurium n=22)	91.3±2.9	12.5±0.6†	10.9±0.3†	26.6±0.4†

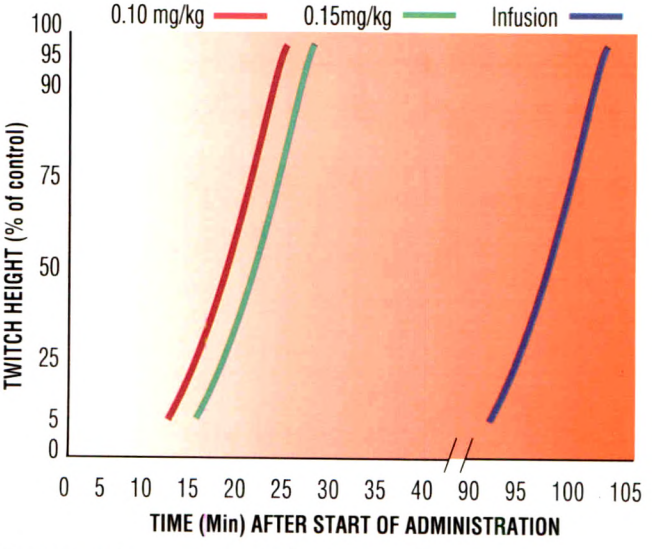
dapted from Ali et al, p. 544.[2] *Time from discontinuation of infusion to 25% recovery. †P<0.01 atracurium or vecuronium vs **M**IVACRON; ‡P<0.001 vecuronium s **M**IVACRON; §P<0.05 vecuronium vs atracurium.

Noncumulative

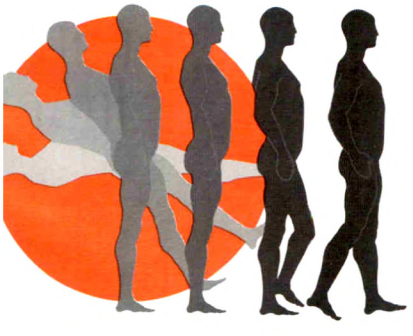
Continuous infusion of **M**IVACRON for up o 2.5 hours is not associated with the development f tachyphylaxis or cumulative neuromuscular locking effects in ASA Physical Status I-II patients. teady-state levels of block are rapidly achieved with inimal adjustment to the infusion rate. Limited data re available on **M**IVACRON (a mixture of three somers) for infusions longer than 2.5 hours.

Savarese et al found...

Fast recovery following bolus or infusion



Adapted from Savarese et al, p. 727.[3]



New MIVACRON® Injection 2 mg/mL (mivacurium chloride)

Short duration, fast recovery

Please see full prescribing information for **M**IVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

New MIVACRON®

Up to half the duration

Excellent cardiovascular profile at recommended doses

MIVACRON Initial Dose* (mg/kg)	% of patients with ≥ 30% changes			
	MAP		HR	
	↓	↑	↓	↑
0.07 to 0.10	0%	2%	0%	0%
0.15	4%	4%	4%	2%
0.20†	30%	0%	0%	8%
0.25†	39%	2%	0%	14%

*During opioid/N_2O/O_2 anesthesia.
†Experimental dose, in excess of the maximum recommended dose of 0.15 mg/kg.

Minimal CV effects

At the recommended initial dose of 0.15 mg/kg, cardiovascular response to **M**IVACRON is minimal. Higher doses may produce effects associated with histamine release and may result in a decrease in blood pressure in some individuals. The incidence and magnitude of these hemodynamic changes are related to size of the dose and speed of the injection. In patients with clinically significant CV disease, the initial dose of **M**IVACRON should be administered over 60 seconds.

Metabolized by plasma cholinesterase

Like succinylcholine, **M**IVACRON should be used with caution in patients with reduced plasma cholinesterase activity. In patients heterozygous for the atypical plasma cholinesterase gene, clinically effective duration may be prolonged by approximately 10 minutes. Homozygous patients (1 in 2500) are *extremely sensitive* to **M**IVACRON. **M**IVACRON should be used with great caution, if at all, in homozygous patients.

However, unlike succinylcholine, once recovery has begun, **M**IVACRON can be reversed with conventional doses of neostigmine.

Individualization of dosages

- Significant CV disease
- Obesity
- Renal or hepatic disease
- History suggesting greater sensitivity to release of histamine or related mediators

from Burroughs Wellcome Co.

half the recovery time

A nondepolarizing alternative to succinylcholine for elective outpatient surgery

	n	Time to max. block (min)*	Time to recovery of T_1=10% (min)*
succinylcholine 1.0 mg/kg	9	1.1±0.2	7.7±1.4
MIVACRON 0.15 mg/kg	8	**2.5**±0.9	**15.6**±3.4

Adapted from Caldwell et al, p.395.[1] *P<0.05 succinylcholine vs MIVACRON.

Caldwell et al concluded...

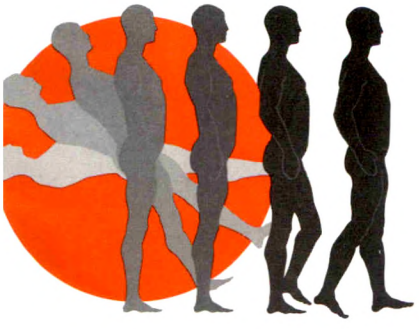
"...in those clinical situations in which rapid onset of action is not required, mivacurium is an alternative to [succinylcholine] for production of profound neuromuscular block of short duration."[p.398]

Plus...

- For use by bolus or infusion
- Ready-to-use solution
- Room temperature storage
- Available in 5 mL and 10 mL vials (2 mg/mL) and 50 mL premixed infusion bags (0.5 mg/mL)

REFERENCES

1. Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth.* 1989;63:393-399.
2. Ali HH, Savarese JJ, Embree PB, et al. Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. *Br J Anaesth.* 1988;61:541-546.
3. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology.* 1988;68:723-732.



New

MIVACRON® Injection 2 mg/mL

(mivacurium chloride)

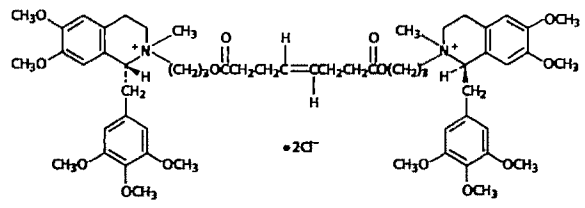
Short duration, fast recovery

Please see full prescribing information for MIVACRON® and brief summary for Tracrium® (atracurium besylate) following this ad.

MIVACRON® INJECTION
MIVACRON PREMIXED INFUSION
(MIVACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: MIVACRON (mivacurium chloride) is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Mivacurium chloride is [*R*-[*R**,*R**-(*E*)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18. The structural formula is:



The partition coefficient of the compound is 0.015 in a 1-octanol/distilled water system at 25°C.

Mivacurium chloride is a mixture of three stereoisomers: (1*R*, 1'*R*, 2*S*, 2'*S*), the *trans-trans* diester; (1*R*, 1'*R*, 2*R*, 2'*S*), the *cis-trans* diester; and (1*R*, 1'*R*, 2*R*, 2'*R*), the *cis-cis* diester. The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers.

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. MIVACRON Premixed Infusion is a sterile, non-pyrogenic solution (pH 3.5 to 5.0; 260 mOsmol/L-measured) containing mivacurium chloride equivalent to 0.5 mg/mL mivacurium in 5% Dextrose Injection USP. Hydrochloric acid may have been added to adjust pH.

CLINICAL PHARMACOLOGY: MIVACRON (a mixture of three stereoisomers) binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: The time to maximum neuromuscular block is similar for recommended doses of MIVACRON and intermediate-acting agents (*e.g.*, atracurium), but longer than for the ultra-short-acting agent, succinylcholine. The clinically effective duration of action of the stereoisomers in MIVACRON (a mixture of three stereoisomers) is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of succinylcholine.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.06 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of doses of MIVACRON ≥ED_{95} administered over 5 to 15 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n=32) following an initial dose of 0.15 mg/kg MIVACRON and 7 to 8 minutes (range: 4 to 24, n=85) following initial doses of 0.20 or 0.25 mg/kg MIVACRON.

Volatile anesthetics may decrease the dosing requirement for MIVACRON and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration]) may decrease the effective dose of MIVACRON by as much as 25%, and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. At equivalent MAC values, halothane has little or no effect on the ED_{50} of MIVACRON, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY and Drug Interaction subsection of PRECAUTIONS).

Table 1
Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		Time to Maximum Block[1] (min)	Time to Spontaneous Recovery[1] 5% Recovery (min)	25% Recovery[2] (min)	95% Recovery[3] (min)	T_4/T_1 Ratio ≥ 75%[3] (min)
Adults						
0.07 to 0.10	[n=47]	4.9 (2.0-7.6)	11 (7-19)	13 (8-24)	21 (10-36)	21 (10-36)
0.15	[n=50]	3.3 (1.5-8.8)	13 (6-31)	16 (9-38)	26 (16-41)	26 (15-45)
0.20	[n=50]	2.5 (1.2-6.0)	18 (10-29)	20 (10-36)	31 (15-51)	34 (19-56)
0.25	[n=48]	2.3 (1.0-4.8)	19 (11-29)	23 (14-38)	34 (22-64)	43 (26-75)
Children 2 to 12 Years						
0.11 to 0.12	[n=17]	2.8 (1.2-4.8)	5 (3-9)	7 (4-10)	–	–
0.20	[n=18]	1.9 (1.3-3.3)	7 (3-12)	10 (6-15)	19 (14-26)	16 (12-23)
0.25	[n=9]	1.6 (1.0-2.2)	7 (4-9)	9 (5-12)	–	–

[1]Values shown are medians of means from individual studies (range of individual patient values).
[2]Clinically effective duration of neuromuscular block.
[3]Data available for as few as 40% of adults in specific dose groups and for 22% of children in the 0.20 mg/kg dose group due to administration of reversal agents or additional doses of MIVACRON prior to 95% recovery or T_4/T_1 ratio recovery to ≥75%.

Administration of MIVACRON over 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of the stereoisomers in MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see Reduced Plasma Cholinesterase Activity subsection of PRECAUTIONS and Individualization of Dosages subsection of CLINICAL PHARMACOLOGY).

Interpatient variability in duration of action occurs with MIVACRON as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of MIVACRON during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery indicated that approximately 90% of the patients had clinically effective durations of block within 8 minutes of the median duration predicted from the dose-response data shown in Table 1. Variations in plasma cholinesterase activity, including values within the normal range and values as low as 20% below the lower limit of the normal range, were not associated with clinically significant effects on duration. The variability in duration, however, was greater in patients with plasma cholinesterase activity at or slightly below the lower limit of the normal range.

A dose of 0.15 mg/kg (2 x ED_{95}) MIVACRON administered during the induction of thiopental/opioid/nitrous oxide/oxygen anesthesia produced generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Doses of 0.20 and 0.25 mg/kg (3 and 3.5 x ED_{95}) yielded similar conditions in 2.0 minutes.

Repeated administration of maintenance doses or continuous infusion of MIVACRON for up to 2.5 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Limited data are available from patients receiving infusions for longer than 2.5 hours. Spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).

The neuromuscular block produced by the stereoisomers in MIVACRON is readily antagonized by anticholinesterase agents. As seen with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

In children (2 to 12 years), MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, and shorter duration of action than in adults. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 5 minutes (n=4) following an initial dose of 0.20 mg/kg MIVACRON. Recovery following reversal is faster in children than in adults (Table 1).

Hemodynamics: Administration of MIVACRON in doses up to and including 0.15 mg/kg (2 x ED_{95}) over 5 to 15 seconds to ASA Physical Status I-II patients during opioid/nitrous oxide/oxygen anesthesia is associated with minimal changes in mean arterial blood pressure (MAP) or heart rate (HR) (Table 2).

Table 2
Cardiovascular Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		% of Patients With ≥30% Change MAP Dec	MAP Inc	HR Dec	HR Inc
Adults					
0.07 to 0.10	[n=49]	0%	2%	0%	0%
0.15	[n=53]	4%	4%	4%	2%
0.20	[n=53]	30%	0%	0%	8%
0.25	[n=44]	39%	2%	0%	14%
Children 2 to 12 years					
0.11 to 0.12	[n=17]	0%	6%	0%	0%
0.20	[n=17]	0%	0%	0%	0%
0.25	[n=8]	13%	0%	0%	0%

Higher doses of ≥0.20 mg/kg (≥3 x ED_{95}) may be associated with transient decreases in MAP and increases in HR in some patients. These decreases in MAP are usually maximal within 1 to 3 minutes following the dose, typically resolve without treatment in an additional 1 to 3 minutes, and are usually associated with increases in plasma histamine concentration. Decreases in MAP can be minimized by administering MIVACRON over 30 or 60 seconds (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY and General subsection of PRECAUTIONS).

Analysis of 426 patients in clinical studies receiving initial doses of MIVACRON up to and including 0.30 mg/kg (*i.e.*, 2 times the recommended intubating dose) during opioid/nitrous oxide/oxygen anesthesia showed that high initial doses and a rapid rate of injection contributed to a greater probability of experiencing a decrease of ≥ 30% in MAP after MIVACRON administration. Obese patients also had a greater probability of experiencing a decrease of ≥30% in MAP when dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight (see Individualization of Dosages subsection of CLINICAL PHARMACOLOGY and the General subsection of PRECAUTIONS).

Children experience minimal changes in MAP or HR after administration of MIVACRON doses up to and including 0.20 mg/kg over 5 to 15 seconds, but higher doses (≥0.25 mg/kg) may be associated with transient decreases in MAP (Table 2).

Following a dose of 0.15 mg/kg MIVACRON administered over 60 seconds, adult patients with significant cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures showed no clinically important changes in MAP or HR. Transient decreases in MAP were observed in some patients after doses of 0.20 to 0.25 mg/kg MIVACRON administered over 60 seconds. The number of patients in whom these decreases in MAP required treatment was small.

Pharmacokinetics: Table 3 describes the results from a study of 9 ASA Physical Status I-II adult patients (31 to 48 years) receiving an infusion of MIVACRON at 5 µg/kg/min for 60 minutes followed by 10 µg/kg/min for 60 minutes. MIVACRON is a mixture of isomers which do not interconvert *in vivo*. The mivacurium pharmacokinetic parameters presented in Table 3 were determined using a stereospecific assay. The two more potent isomers, *cis-trans* (36% of the mixture) and *trans-trans* (57% of the mixture), have very high clearances that exceed cardiac output reflecting the extensive metabolism by plasma cholinesterase. The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The combination of high metabolic clearance and low distribution volume results in the short elimination half-life of approximately 2 minutes for the two active isomers. The short elimination half-lives and high metabolic clearances of the active isomers are consistent with the short duration of action of MIVACRON. The steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled after the infusion rate was increased from 5 to 10 µg/kg/min, indicating that their pharmacokinetics are dose-proportional.

Table 3
Stereoisomer Pharmacokinetic Parameters[1] of MIVACRON in ASA Physical Status I-II Adult Patients[2] [n=9] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* Isomer	*cis-trans* Isomer
Elimination Half-life ($t_{1/2}$, min)	2.3 (1.4-3.6)	2.1 (0.8-4.8)
Volume of Distribution (L/kg)	0.15 (0.06-0.24)	0.27 (0.08-0.56)
Plasma Clearance (mL/min/kg)	53 (32-105)	99 (52-230)

[1]Values shown are mean (range).
[2]Ages 31 to 48 years.

The *cis-cis* isomer (8% of the mixture) has approximately one-tenth the neuromuscular blocking potency of the

trans-trans and *cis-trans* isomers in cats. In the nine patients shown in Table 3, the volume of distribution of the *cis-cis* isomer averaged 0.31 L/kg (range: 0.18-0.46), the clearance averaged 4.2 mL/min/kg (range: 2.4-5.4), and the half-life averaged 55 minutes (range: 32-102). The neuromuscular blocking potency of the *cis-cis* isomer in humans has not been established; however, modeling of clinical pharmacokinetic-pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a two-hour infusion. In studies in which infusions of up to 2.5 hours were administered to ASA Physical Status I–II patients, the 25%-75% recovery times were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not contribute significant neuromuscular block during use for up to 2.5 hours. Limited data are available from infusions of longer duration or from patients with compromised elimination capacities (hepatic or renal failure).

Metabolism and Excretion: *Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite.* Renal and biliary excretion of unchanged mivacurium are minor elimination pathways; urine and bile are important elimination pathways for the two metabolites. Tests in which these two metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of MIVACRON.

Special Populations: The pharmacokinetics of mivacurium isomers has not been studied in the elderly or in patients with renal or hepatic disease using a stereospecific assay. The non-stereospecific, total mivacurium assay used in pharmacokinetic-pharmacodynamic studies in these populations provided preliminary evidence that reduced clearance of one or more isomers is responsible for the longer duration of action of MIVACRON seen in patients with end-stage kidney or liver disease. The data did not provide a pharmacokinetic explanation for the 15-20% longer duration of block seen in the elderly. Tables 4 and 5 summarize the pharmacodynamic results in these special populations as compared with young adults (ages 18 to 49 years). No data are available from patients with kidney or liver disease not requiring transplantation.

Table 4
Pharmacodynamic Parameters[1] of MIVACRON In ASA Physical Status I-II Young Adult Patients and Elderly Patients During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients (18-49 years)		Elderly Patients (68-77 years)
Initial Dose	0.10 mg/kg [n=9]	0.25 mg/kg [n=9]	0.10 mg/kg [n=8]
Maximum Block (%)	98 (83-100)	100 (100-100)	99 (95-100)
Time to Maximum Block (min)	3.2 (2.0-6.0)	1.7 (1.3-2.5)	4.8 (3.0-7.0)
Clinically Effective Duration of Block[2] (min)	17 (9-29)	27 (18-34)	20 (14-28)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.

Renal: The clinically effective duration of action of 0.15 mg/kg MIVACRON was about 1.5 times longer in patients with end-stage kidney disease than in healthy patients, presumably due to reduced clearance of one or more isomers.

Hepatic: The clinically effective duration of action of 0.15 mg/kg MIVACRON was three times longer in patients with end-stage liver disease than in healthy patients and is likely related to the markedly decreased plasma cholinesterase activity (30% of healthy patient values) which could decrease the clearance of one or more isomers (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Table 5
Pharmacodynamic Parameters[1] of MIVACRON In ASA Physical Status I-II Patients and In Patients Undergoing Kidney or Liver Transplantation During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

Parameter	Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients[3]
Initial Dose	0.15 mg/kg [n=8]	0.15 mg/kg [n=9]	0.15 mg/kg [n=8]
Maximum Block (%)	99.8 (98-100)	100 (100-100)	100 (100-100)
Time to Maximum Block (min)	1.9 (0.8-3.5)	2.6 (1.0-4.5)	2.1 (1.0-4.0)
Clinically Effective Duration of Block[2] (min)	19 (12-30)	30 (19-58)	57 (29-80)

[1]Values shown are mean (range).
[2]Time from injection to 25% recovery of the control twitch height.
[3]Liver transplant patients received isoflurane without nitrous oxide.

ndividualization of Dosages: DOSES OF MIVACRON SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING MIVACRON ADMINISTRATION IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

Based on the known actions of MIVACRON (a mixture of three stereoisomers) and other neuromuscular blocking agents, the following factors should be considered when administering MIVACRON:

Renal or Hepatic Impairment: A dose of 0.15 mg/kg MIVACRON is recommended for facilitation of tracheal intubation in patients with renal or hepatic impairment. However, the clinically effective duration of block produced by this dose is about 1.5 times longer in patients with end-stage kidney disease and about 3 times longer in patients with end-stage liver disease than in patients with normal renal and hepatic function. Infusion rates should be decreased by as much as 50% in these patients depending on the degree of renal or hepatic impairment (see **Renal and Hepatic Disease** subsection of PRECAUTIONS).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. MIVACRON should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of MIVACRON are not recommended in homozygous patients.

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After recommended intubating doses of MIVACRON, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower MIVACRON infusion rates are recommended in these patients (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Drugs or Conditions Causing Potentiation of or Resistance to Neuromuscular Block: As with other neuromuscular blocking agents, MIVACRON may have profound neuromuscular blocking effects in cachectic or debilitated patients, patients with neuromuscular diseases, and patients with carcinomatosis. In these or other patients in whom potentiation of neuromuscular block or difficulty with reversal may be anticipated, the recommended initial dose should be decreased. A test dose of not more than 0.015–0.020 mg/kg, which represents the lower end of the dose-response curve for MIVACRON, is recommended in such patients (see **General** subsection of PRECAUTIONS).

The neuromuscular blocking action of the stereoisomers in MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used for intubation prior to the administration of these agents. If MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose should be reduced by as much as 25%, and the infusion rate reduced by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking action of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. The use of halothane requires no adjustment of the initial dose of MIVACRON, but may prolong the duration of action and decrease the average infusion rate by as much as 20% (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients receiving certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide and quinidine, longer durations of neuromuscular block may be expected and infusion requirements may be lower (see **Drug Interactions** subsection of PRECAUTIONS).

When MIVACRON is administered to patients chronically receiving phenytoin or carbamazepine, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher (see **Drug Interactions** subsection of PRECAUTIONS).

Severe acid-base and/or electrolyte abnormalities may potentiate or cause resistance to the neuromuscular blocking action of the stereoisomers in MIVACRON. No data are available in such patients and no dosing recommendations can be made (see **General** subsection of PRECAUTIONS).

Burns: While patients with burns are known to develop resistance to nondepolarizing neuromuscular blocking agents, they may also have reduced plasma cholinesterase activity. Consequently, in these patients, a test dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended, followed by additional appropriate dosing guided by the use of a neuromuscular block monitor (see **General** subsection of PRECAUTIONS).

Cardiovascular Disease: In patients with clinically significant cardiovascular disease, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS).

Obesity: Obese patients (patients weighing ≥30% more than their ideal body weight) dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight, had a greater probability of experiencing a decrease of ≥30% in MAP (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY and **General** subsection of PRECAUTIONS). Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2
Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Allergy and Sensitivity: In patients with any history suggestive of a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma), the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see **General** subsection of PRECAUTIONS).

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multi-dose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see **Pharmacokinetics** subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene); pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED_{10-30} in genotypically normal patients) produced complete neuromuscular block for 26 to 126 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereoisomers in MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{50} of MIVACRON by as much as 25% (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of MIVACRON by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{50}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neuromuscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomers in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRON revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of MIVACRON in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see **General** subsection of PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients than in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who received the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. None of the 397 adults or 63 children who received recommended doses was treated for a decrease in blood pressure associated with the administration of MIVACRON. Above the recommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see **Antagonism of Neuromuscular Block**). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or especially cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

Initial Doses:

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

In patients with clinically significant cardiovascular disease and in patients with any history suggesting a greater sensitivity to the release of histamine or other mediators (*e.g.*, asthma), the dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS).

Clinically effective neuromuscular block may be expected to last for 15 to 20 minutes (range: 9 to 36) and spontaneous recovery may be expected to be 95% complete in 25 to 30 minutes (range: 16 to 41) following 0.15 mg/kg MIVACRON administered to patients receiving opioid/nitrous oxide/oxygen anesthesia. Maintenance dosing is generally required approximately 15 minutes following an initial dose of 0.15 mg/kg MIVACRON during opioid/nitrous oxide/oxygen anesthesia. Maintenance doses of 0.10 mg/kg each provide approximately 15 minutes of additional clinically effective block. For shorter or longer durations of action, smaller or larger maintenance doses may be administered.

The neuromuscular blocking action of MIVACRON is potentiated by isoflurane or enflurane anesthesia. The recommended initial MIVACRON dose of 0.15 mg/kg may be used to facilitate tracheal intubation prior to the administration of these agents; however, if MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial MIVACRON dose may be reduced by as much as 25%. Greater reductions in the MIVACRON dose may be required with higher concentrations of enflurane or isoflurane. With halothane, which has only a minimal potentiating effect on MIVACRON, a smaller dosage reduction may be considered.

Continuous Infusion: Continuous infusion of MIVACRON may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial dose, an initial infusion rate of 9 to 10 µg/kg/min is recommended. If continuous infusion is initiated simultaneously with the administration of an initial dose, a lower initial infusion rate should be used (*e.g.*, 4 µg/kg/min). In either case, the initial infusion rate should be adjusted according to the response to peripheral nerve stimulation and to clinical criteria. On average, an infusion rate of 6 to 7 µg/kg/min (range: 1 to 15) may be expected to maintain neuromuscular block within the range of 89% to 99% for extended periods in adults receiving opioid/nitrous oxide/oxygen anesthesia. Reduction of the infusion rate by up to 35% to 40% should be considered when MIVACRON is administered during stable-state conditions of isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC). Greater reductions in the MIVACRON infusion rate may be required with greater concentrations of enflurane or isoflurane. With halothane, smaller reductions in infusion rate may be required.

Children:

Initial Doses: Dosage requirements for MIVACRON on a mg/kg basis are higher in children than adults. Onset and recovery of neuromuscular block occur more rapidly in children than adults (see CLINICAL PHARMACOLOGY). The recommended dose of MIVACRON for facilitating tracheal intubation in children 2 to 12 years of age is 0.20 mg/kg administered over 5 to 15 seconds. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.20 mg/kg of MIVACRON produces maximum neuromuscular block in an average of 1.9 minutes (range: 1.3 to 3.3) and clinically effective block for 10 minutes (range: 6 to 15). Maintenance doses are generally required more frequently in children than in adults. Administration of MIVACRON doses above the recommended range (>0.20 mg/kg) is associated with transient decreases in MAP in some children (see **Hemodynamics** subsection of CLINICAL PHARMACOLOGY). MIVACRON has not been studied in children below the age of 2 years.

Continuous Infusion: Children require higher MIVACRON infusion rates than adults. During opioid/nitrous oxide/oxygen anesthesia the infusion rate required to maintain 89% to 99% neuromuscular block averages 14 µg/kg/min (range: 5 to 31). The principles for infusion of MIVACRON in adults are also applicable to children (see above).

Infusion Rate Tables:

For adults and children the amount of infusion solution required per hour depends upon the clinical requirements of the patient, the concentration of MIVACRON in the infusion solution, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient must be considered. Tables 6 and 7 provide guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of MIVACRON Premixed Infusion (0.5 mg/mL) and of MIVACRON Injection (2 mg/mL).

Table 6
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Premixed Infusion (0.5 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	5	6	7	8	10	12	17	19	22	24
15	7	9	11	13	14	18	25	29	32	36
20	10	12	15	17	19	24	34	38	43	48
25	12	15	18	21	24	30	42	48	54	60
35	17	21	26	29	34	42	59	67	76	84
50	24	30	36	42	48	60	84	96	108	120
60	29	36	43	50	58	72	101	115	130	144
70	34	42	50	59	67	84	118	134	151	168
80	39	48	58	67	77	96	134	154	173	192
90	44	54	65	76	86	108	151	173	194	216
100	48	60	72	84	96	120	168	192	216	240

Table 7
Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON Injection (2 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	1.2	1.5	1.8	2.1	2.4	3.0	4.2	4.8	5.4	6.0
15	1.8	2.3	2.7	3.2	3.6	4.5	6.3	7.2	8.1	9.0
20	2.4	3.0	3.6	4.2	4.8	6.0	8.4	9.6	10.8	12.0
25	3.0	3.8	4.5	5.3	6.0	7.5	10.5	12.0	13.5	15.0
35	4.2	5.3	6.3	7.4	8.4	10.5	14.7	16.8	18.9	21.0
50	6.0	7.5	9.0	10.5	12.0	15.0	21.0	24.0	27.0	30.0
60	7.2	9.0	10.8	12.6	14.4	18.0	25.2	28.8	32.4	36.0
70	8.4	10.5	12.6	14.7	16.8	21.0	29.4	33.6	37.8	42.0
80	9.6	12.0	14.4	16.8	19.2	24.0	33.6	38.4	43.2	48.0
90	10.8	13.5	16.2	18.9	21.6	27.0	37.8	43.2	48.6	54.0
100	12.0	15.0	18.0	21.0	24.0	30.0	42.0	48.0	54.0	60.0

MIVACRON Premixed Infusion in Flexible Plastic Containers:

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

Instructions for Use:

1. Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired.
2. Close flow control clamp of administration set.
3. Remove cover from outlet port at bottom of container.
4. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
5. Suspend container from hanger.
6. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion.
7. Open flow control clamp to expel air from set. Close clamp.
8. Attach set to intravenous tubing.
9. Regulate rate of administration with flow control clamp.

Caution: Additives should not be introduced into this solution. Do not administer unless solution is clear and container is undamaged. MIVACRON Premixed Infusion is intended for single patient use only. The unused portion of the solution should be discarded.

Warning: Do not use flexible plastic container in series connections.

MIVACRON Injection Compatibility and Admixtures:

Y-site Administration: MIVACRON Injection may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Studies have shown that MIVACRON Injection is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose in Lactated Ringer's Injection
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed
- Versed® (midazolam hydrochloride) Injection, diluted as directed
- Inapsine® (droperidol) Injection, diluted as directed

Compatibility studies with other parenteral products have not been conducted.

Dilution Stability: MIVACRON Injection diluted to 0.5 mg mivacurium per mL in 5% Dextrose Injection USP, 5% Dextrose and 0.9% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, Lactated Ringer's Injection USP, or 5% Dextrose in Lactated Ringer's Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at 5°C to 25°C (41°F to 77°F) for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of MIVACRON should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted MIVACRON should be discarded after each case.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear and colorless should not be used.

HOW SUPPLIED: MIVACRON Injection, 2 mg mivacurium in each mL.

5 mL Single Use Vials. Tray of 10 (NDC 0081-0705-44).

10 mL Single Use Vials. Tray of 10 (NDC 0081-0705-95).

MIVACRON Premixed Infusion in 5% Dextrose Injection USP, 0.5 mg mivacurium in each mL.

50 mL (in a 100 mL unit) Flexible Plastic Containers. (NDC 0081-0709-01).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418 554053

MIVACRON Premixed Infusion Manufactured for BURROUGHS WELLCOME CO. by Abbott Laboratories

---

TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL **single** use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

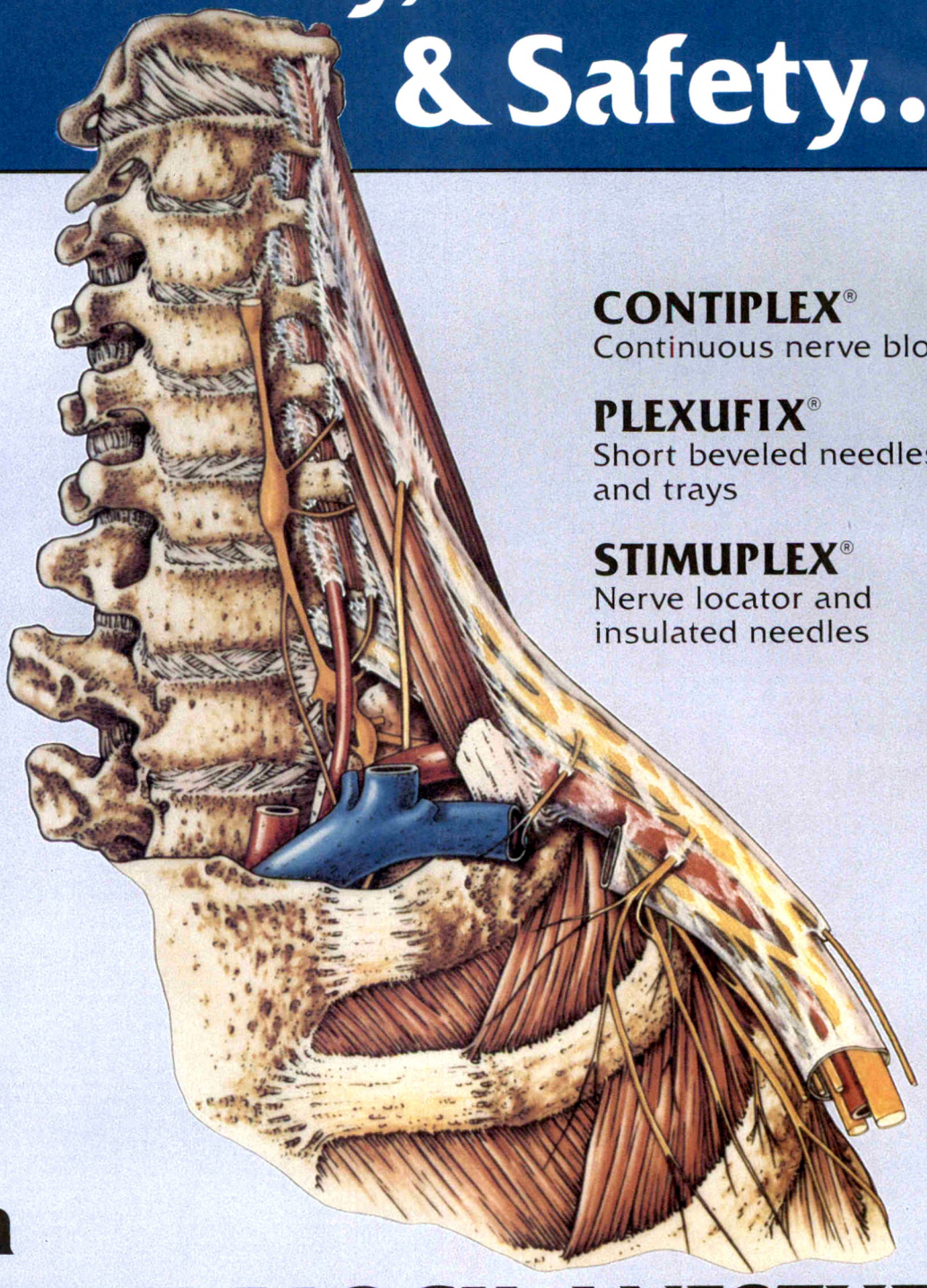
ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.5% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Wellcome Copr. © 1992 Burroughs Wellcome Co. All rights reserved. MV-Y03552

Accuracy, Precision & Safety...



CONTIPLEX®
Continuous nerve block

PLEXUFIX®
Short beveled needles and trays

STIMUPLEX®
Nerve locator and insulated needles

in NERVE BLOCK ANESTHESIA

BURRON MEDICAL INC.
824 Twelfth Avenue
Bethlehem, PA 18018
800-523-9695 / 215-691-5400
B. Braun of America Company

B.BRAUN



Be Prepared for Malignant Hyperthermia

Fatalities resulting from malignant hyperthermia are **unexpected, unfair** and almost always, **unnecessary.**

Unexpected because the patient - child or adult - shows no outward signs of this genetic disorder. And there is no simple diagnostic test. Most people have never heard of malignant hyperthermia **until** it strikes.

Unfair because it is triggered by the patient's reaction to certain common anesthetics used during surgery. The life-threatening episode that results has nothing whatsoever to do with the condition requiring the surgery.

Unnecessary, in most cases, because preparedneess and prompt treatment can arrest the episode before it reaches dangerous levels. Persons who know of their susceptibility can have surgery safely using non-triggering anesthetics. When MH strikes unexpectedly during an operation, it can be brought under control by early diagnosis and immediate treatment.

As a medical professional, you can combat this silent killer. For the latest information on diagnosing and treating malignant hyperthermia, contact the Malignant Hyperthermia Association of the United States (MHAUS) at (203) 655-3007. It may mean the difference between life or death.

MHAUS
P.O. Box 191
Westport, CT 06881-0191

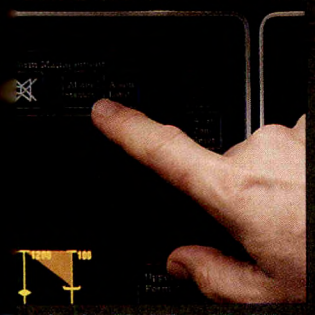
Picture your patient in 3D

The Modulus® CD-CV from Ohmeda is the first anesthesia system to bring you truly integrated, comprehensive patient status monitoring. By uniting today's most advanced monitoring capabilities in a single array, the system allows you to simultaneously view three crucial dimensions of patient response to anesthesia: *cardiovascular, respiratory* and *ventilatory*.

And because all three are integral to the anesthesia system itself, you manage them all at one time.

Scanning the display screen positioned near your patient, you see ECG, invasive BP, temperature and NIBP information alongside respiratory gas data, volumes and airway pressures. This wealth of data is logically grouped and prioritized to help you readily correlate values and observe variances in your patient's condition.

You can, for example, view combinations of data, such as ECG, SpO_2, P_{AW} and CO_2 for general monitoring. Or, when you feel a more detailed diagnostic approach is indicated, you can instantly convert the display to dedicated ECG, ventilation or pressure data to hone in on the specific parameters you want to examine. If you add an arterial line during a case, the Modulus CD-CV automatically reformats its displays to accommodate this new data.



Touch, the Modulus CD-CV silence, or place into standby system alarms.

The unique simplicity of the Modulus CD-CV also means you define alarm limits – once – from a single display, then save your personal preferences for future cases. And with one keystroke, you silence or place all monitors, physiologic and machine status, in standby. You can then proceed to intubate, correct problems, and concentrate on caring for your patient without the distraction of nuisance alarms.

A platform for expansion.

The cardiovascular monitoring package, also available for current Modulus CD Systems, demonstrates Ohmeda's delivery of ongoing upgrades to keep your system up to date... cost effectively. In fact, the CV monitoring package is itself upgradeable to accommodate future options.

To learn how the integrated Modulus CD-CV helps you picture your patient in 3D – cardiovascular, respiratory and ventilatory – contact your Ohmeda representative or call 1-800-345-2700.

Ohmeda. A world of choice in anesthesia.

©1993 BOC Health Care Inc. D745


Management
Alarm Standby
Alarm Limits
Alert Zone On/Off
Alert Zone Reset
Alert Zone Limits
Upper Display Format
123 Numeric
Art1 mmHg
119
80
(92)
PAP mmHg
25
11
(15)
86
12
Temp
T1 36.9
T2 37.0
Vol
VE 7.3
Paw
max 13
min 2
Iso
I 1.7
E 1.6
N2O
68
O2
I 23
SpO2
00
CO2 mmHg
35
Primary Display
180
120
60
30
20
10
0
60
40
20
0
II
60
Abn/min 0
ART1
119/ 80
(92)
PAP
25/ 11
(15)
CO2
Lower Display Selection
Primary Display Config
Primary Display
ECG
Graphic Trend
Pressure
Digital Trend
Vent
Ohmeda
Ohmeda
Ohmeda Drive
7550 USA
A BOC Health Care Company
Critical Care Worldwide



Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents**[1-5]
- **A smooth induction**[5]
- **Less risk of breakthrough awareness**[5]
- **A smooth emergence**[5]

Dosing considerations

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE

VERSED®

midazolam HCl/Roche Ⓘⓥ

FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284.

VERSED®
midazolam HCl/Roche ®
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.) The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.
Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.
WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.
Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.
Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.
Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.
Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.
Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.
Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.
VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.
Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.
Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.
PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.
VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.
Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.
Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.
A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.
IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.
Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.
No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.
Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.
Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.
Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.
Midazolam did not have mutagenic activity in tests that were conducted.
A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.
Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.
Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.
Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.
Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.
Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.
ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.
Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).
IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.
Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.8%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.
Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.
OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0691

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Bupivacaine Toxicity Secondary to Continuous Caudal Epidural Infusion in Children

John J. McCloskey, MD, Steven E. Haun, MD, and Jayant K. Deshpande, MD

Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Hospital, Baltimore, Maryland; Department of Pediatrics, Children's Hospital, Columbus, Ohio; and Department of Pediatrics and Anesthesiology, Vanderbilt University, Nashville, Tennessee

Regional anesthesia has become an integral part of the intraoperative anesthetic management of children (1,2). The success of nerve blocks and "kiddie caudals" in managing surgical stress has also led to the use of these techniques in alleviating postoperative pain (2–5). In many instances, bupivacaine is the local anesthetic chosen for these techniques because of its longer duration of action and greater sensory versus motor blockade at a given therapeutic dose (6,7). A safe and effective bolus dose for caudal injection, based on pharmacokinetic and pharmacodynamic studies, has been determined for infants and children (8–10); however, the pharmacokinetic and pharmacodynamic properties of prolonged continuous caudal epidural bupivacaine infusions in children have not been investigated.

We present three case reports to illustrate that prolonged infusions of bupivacaine by the caudal route can lead to systemic toxicity.

Case 1

A 3.89-kg full-term male neonate was noted to have exstrophy of the bladder at birth. No other abnormalities were noted on physical examination. On day 1 of life, the bladder defect was closed under general anesthesia supplemented with a caudal epidural block. A catheter was placed in the caudal epidural space under sterile conditions. After testing for proper placement of the catheter, a 4-mL bolus dose of 0.25% bupivacaine (2.5 mg/kg) with 1:200,000 epinephrine was infused through the catheter without complication. An adequate block was assumed because the need for inhaled anesthetic decreased during the course of the procedure. The child received 3 mL (1.87 mg/kg) of the same bupivacaine solution at 1.5 and 3 h after the initial bolus dose. The patient emerged from general anesthesia without complication and was taken to the pediatric intensive care unit for observation and pain management via the caudal catheter.

Approximately 1.5 h after his last intraoperative dose of bupivacaine, an infusion of 0.25% bupivacaine with 1:200,000 epinephrine was initiated at a rate of 4 mL/h (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$). Ten hours after starting the infusion, the patient developed bradycardia with resultant hypotension. The bupivacaine infusion was stopped, and bag and mask ventilation with chest compressions was started. His trachea was intubated. Epinephrine (10 $\mu g/kg$) was given intravenously, and the rhythm quickly changed from sinus bradycardia (heart rate 40 beats/min) to ventricular tachycardia. This rhythm was partially responsive to three bolus doses of intravenous lidocaine (1 mg/kg) and sodium bicarbonate (1 mEq/kg). Normal sinus rhythm was established after intravenous infusion of phenytoin (5 mg/kg). Two hours later, ventricular tachycardia recurred along with the development of generalized tonic-clonic seizures. The patient was normotensive during this period. Two doses of bretylium (2 mg/kg IV) were administered without a change in the cardiac rhythm. Treatment with diazepam (0.25 mg/kg IV) and phenytoin (7 mg/kg IV) aborted the seizures and ventricular tachycardia. The trachea was extubated approximately 24 h later. Examination at that time and over the course of his hospitalization revealed no obvious neurologic sequelae.

A total serum bupivacaine level drawn immediately after the initial episode of ventricular tachycardia was subsequently reported as 5.6 $\mu g/mL$, and a second level 12 h after the initial episode was 3.7 $\mu g/mL$.

Case 2

An 8-yr-old, 45-kg (ASA physical status I) girl with a history of multiple surgical procedures for bladder exstrophy presented for bladder augmentation and

Accepted for publication March 11, 1992.

Address correspondence to Dr. McCloskey, A.I. duPont Institute for Children, Department of Anesthesiology/Critical Care Medicine, P.O. Box 269, 1600 Rockland Road, Wilmington, DE 19899.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

bilateral ureteral implantation. General anesthesia was induced with sodium thiamylal, O_2, N_2O, and isoflurane. After induction, a 20-gauge epidural catheter was placed in the caudal space. After assuring proper placement, a 25-mL bolus dose of 0.25% bupivacaine (1.4 mg/kg) with 1:200,000 epinephrine was infused without complication. During the surgical procedure, the patient subsequently received 0.83, 0.55, and 1 mg/kg of 0.25% bupivacaine through the catheter at 1.5, 3.5, and 5.5 h, respectively. The patient emerged from general anesthesia without complication and was transported to the pediatric intensive care unit for monitoring and pain control.

Approximately 4 h after her last intraoperative dose of bupivacaine, a continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine was initiated at a rate of 30 mL/h (1.67 $mg \cdot kg^{-1} \cdot h^{-1}$). The level of sensory anesthesia was assessed at T-10. The infusion was continued at this rate as the level of analgesia remained unchanged. Twenty-five hours after starting the infusion, the patient developed two episodes of generalized tonic-clonic seizure activity. The seizure activity resolved with 0.05 mg/kg of diazepam. Neurologic examination after the seizures revealed no abnormalities. A total serum bupivacaine level drawn shortly thereafter was reported as 6.6 μg/mL.

Case 3

A 4-yr-old, 12-kg girl (ASA physical status I) sustained bilateral knee trauma secondary to a motor vehicle accident. There was no history or physical evidence of head trauma. She was brought to the operating room for irrigation and debridement of her wounds. After induction of general anesthesia with sodium thiamylal and isoflurane in O_2/N_2O, an epidural catheter was placed in the caudal space under sterile conditions. A test dose of local anesthetic was then given without complication. This was followed by a 12-mL bolus injection of 0.25% bupivacaine (2.5 mg/kg) with 1:200,000 epinephrine. During the procedure, she received a bolus injection of 20 mg of bupivacaine (1.67 mg/kg) through the catheter at 2, 4, and 5.5 h after the initial bolus dose. She emerged from general anesthesia without complication and was transported to the pediatric intensive care unit for monitoring and pain management.

Approximately 3 h after the last intraoperative dose of caudal bupivacaine, a continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine was started at 8 mL/h (1.67 $mg \cdot kg^{-1} \cdot h^{-1}$). The sensory level of anesthesia was assessed at T-10. The infusion was continued at the same rate until 26 h after starting the infusion, at which time the level of analgesia (L-2) was significantly diminished. Evaluation of the catheter revealed a small leak just proximal to the skin entry of the catheter. It was removed, and another was placed under sterile conditions. A test dose of 2 mL of 0.25% bupivacaine (0.42 mg/kg) was given through the new catheter without complication. The infusion was restarted at 2.0 $mg \cdot kg^{-1} \cdot h^{-1}$. Approximately 8 h after restarting the infusion (approximately 34 h after starting the first infusion), the patient developed a generalized tonic-clonic seizure. The seizure resolved with diazepam (0.1 mg/kg IV). Neurologic examination after the seizure revealed no abnormalities. During the seizure, the bupivacaine infusion was stopped, and a total serum bupivacaine level was drawn. It was later reported as 10.2 μg/mL.

Discussion

Perioperative surgical stimulation and pain in children can be effectively managed with regional anesthetic techniques (1–5,7,11,12). Single-dose "kiddie caudals" decrease the amount of general anesthetics needed during surgical procedures and can provide pain relief well after a procedure is completed (4,5). Postoperative pain in children can also be attenuated with the use of continuous infusions of local anesthetics via the lumbar epidural and intrapleural routes (11,12). In the majority of these studies, bupivacaine is the local anesthetic of choice (6,7). The pharmacokinetics of bupivacaine by these routes of administration have been evaluated, but there are no studies that have evaluated the pharmacokinetics of bupivacaine with continuous, prolonged infusions in the caudal epidural space. Although the doses of bupivacaine used in the previously mentioned studies were safe and effective, toxic serum levels of bupivacaine can have serious effects on the cardiovascular and central nervous systems (13,14).

Studies by Mazoit et al. (8) and Ecoffey et al. (10) have evaluated the pharmacokinetics of single bolus injections of bupivacaine via the caudal epidural space in infants and children (Table 1). The dose used in these studies (2.5 mg/kg) provided adequate analgesia without producing toxic serum levels. The maximal serum concentration (C_{max}) reported in these studies was similar; however, the elimination half-life ($T_{1/2\beta}$) and volume of distribution (Vd) were greater in the infant age group compared with the child age group. These changes are presumed to be caused by an increase in serum protein binding that occurs with aging.

The rates of administration of continuous bupivacaine infusion used in our patients (1.25–2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) described earlier were extrapolated from bolus dosages routinely used in the operating room for brief procedures. Several studies have demonstrated that bolus doses of bupivacaine at 2.5–3.0 mg/kg in infants and children will produce a C_{max} in the range of

Table 1. Pharmacokinetics of Bolus Caudal Epidural Bupivacaine in Infants and Children

	C_{max} (μg/mL)	T_{max} (min)	$T_{1/2\beta}$ (h)	Vd (L/kg)	Cl (mL·min^{-1}·kg^{-1})
Infants[a] (2.5 mg/kg)	0.97 ± 0.42	28 ± 13	7.7 ± 2.4	3.9 ± 2.0	7.1 ± 3.2
Children[b] (2.5 mg/kg)	1.25 ± 0.09	29.1 ± 3.1	4.6 ± 0.5	2.7 ± 0.2	10.0 ± 0.7

C_{max}, maximal serum concentration; T_{max}, maximal time; $T_{1/2\beta}$, elimination half-life; Vd, volume of distribution; Cl, clearance.
[a]Expressed as value ± SD; Mazoit et al. (8).
[b]Expressed as value ± SEM; Ecoffey et al. (10).

0.22–1.93 μg/mL (8–10); levels far less than the toxic threshold level of 4 μg/mL in adults (15). Thus, it was presumed that these infusion rates would not produce toxic serum levels of bupivacaine; however, each of these patients developed generalized seizures, presumably from systemic accumulation of bupivacaine. In addition, patient 1, a neonate, developed cardiovascular toxicity despite exhibiting a lower serum level of bupivacaine. Infants are at greater risk for bupivacaine toxicity because α_1-acid glycoprotein, the major serum protein to which bupivacaine is bound, is lower in infants compared with older age groups (8). The lower levels of α_1-acid glycoprotein can result in a greater amount of free drug in the serum. The rate of rise in the serum level of bupivacaine may have also influenced the development of relatively greater toxicity in patient 1 because he received a greater concentration of bupivacaine (0.25% vs 0.125%) compared with the other patients. A larger dose was empirically chosen for patient 1 to provide a more dense motor block; it was speculated the more dense block would help prevent wound dehiscence, which has a high rate of occurrence after bladder exstrophy repair in this age group.

With the data from Table 1 and assuming a steady-state serum concentration (Css) of 1.0–1.5 μg/mL, safe and effective rates for continuous bupivacaine infusion though the caudal epidural space can be extrapolated. With constant infusion of drugs at steady state, Css is equal to the rate of infusion (Ro) divided by clearance (Cl). Thus, the rate of infusion is the product of the serum concentration and the clearance (Ro = Cl × Css). The data from Table 1 suggest that an infusion rate of 0.4 mg·kg^{-1}·h^{-1} for infants <6 mo old and a rate of 0.75 mg·kg^{-1}·h^{-1} for older children will probably provide adequate analgesia without causing toxicity: these rates of infusion are far less than what was administered to our patients. These calculated rates, however, are based on linear pharmacokinetics and do not account for possible saturation of local tissue binding sites that may occur with long-term administration of drugs. Richter et al. (16) have demonstrated in adults that continuous epidural infusions follow linear pharmacokinetics until approximately 50 h of infusion, at which time the plasma levels of bupivacaine increase dramatically.

Although the pharmacokinetics of continuous caudal epidural infusion of bupivacaine has not been studied in children, Desparmet et al. (11) have evaluated the pharmacokinetics of continuous lumbar epidural infusion of bupivacaine in children. In that study, 21 patients received a loading dose of 0.25% bupivacaine (1.25 mg/kg); 30 min later, a continuous infusion of 0.25% at a rate of 0.2 mg·kg^{-1}·h^{-1} was instituted. Of these 21 children, 6 (3.5–11 yr) had plasma bupivacaine levels measured during a period 24–48 h after the start of the infusion. The initial sensory level of anesthesia was between T-10 and L-1; only 2 of the 21 children complained of discomfort above the T-12 level. In the six children who had plasma bupivacaine measurements, the Css ranged from 0.30 ± 0.11 to 0.73 ± 0.7 μg/mL, and Cl ranged from 3.96 to 11.11 mL·min^{-1}·kg^{-1}. These values for Css and Cl are similar to values for C_{max} and Cl in single-bolus dose caudal injections (8,10) and thus corroborate the values calculated previously for effective and safe doses of prolonged continuous caudal epidural infusions of bupivacaine.

Compared with the Desparmet et al. (11) study, the McIlvaine et al. (12) study on the use of continuous bupivacaine through an intrapleural catheter for analgesia after thoracotomy in children suggests that a higher concentration of bupivacaine can be used in children. In this study, the pharmacokinetics of a 24-h continuous infusion of intrapleural bupivacaine was evaluated in 14 children, approximately 10.75 ± 6 yr in age, who had a thoracotomy for anterior spinal fusion or aortic coarctation repair. These patients received a concentration of 0.25% bupivacaine with 1:200,000 epinephrine at an initial rate of 0.5 mL·kg^{-1}·h^{-1} (1.25 mg·kg^{-1}·h^{-1}); the rate was increased to a maximum of 1.0 mL·kg^{-1}·h^{-1} (2.5 mg·kg^{-1}·h^{-1}) if analgesia was not judged to be adequate. Over the 24 h, the mean rate of infusion increased to approximately 1.6 ± 0.8 mg·kg^{-1}·h^{-1}. Serum levels in the seven patients who underwent anterior spinal fusion rose from 0.76 ± 0.24 μg/mL at 4 h into the infusion to 4.2 ± 0.72 μg/mL at 24 h. In the seven patients who underwent aortic

coarctation repair, the levels rose from 0.77 ± 0.19 μg/mL at 4 h to 2.47 ± 0.52 μg/mL at 24 h. Five patients had levels >4 μg/mL, and one had a level >7 μg/mL; despite these high levels, no patient developed signs of cardiovascular or central nervous system toxicity. These data, like those of Desparmet et al. (11), also suggest that the calculated infusion rates for continuous caudal epidural infusions should be safe because systemic absorption of local anesthetic from the intrapleural space is greater than from the intercostal space (17), and absorption from the intercostal space is greater than from the caudal epidural space (18). Furthermore, the serum levels of bupivacaine in the McIlvaine et al. (12) study suggest that pediatric patients may have a higher threshold at which bupivacaine toxicity develops than adults.

In summary, we present three cases of bupivacaine toxicity (seizures, hypotension, arrhythmia) secondary to prolonged continuous infusions by caudal administration. The rates of infusion for these patients were chosen empirically because of the paucity of pharmacokinetic studies involving the use of prolonged continuous caudal epidural infusions in infants and children. Analysis of pharmacokinetic studies involving bolus caudal infusions and prolonged continuous lumbar epidural infusions in children would suggest that infusion rates of 0.2–0.4 $mg \cdot kg^{-1} \cdot h^{-1}$ in infants and 0.2–0.75 $mg \cdot kg^{-1} \cdot h^{-1}$ in children may be effective without producing toxicity. Therefore, it seems prudent to use such doses when considering prolonged continuous caudal infusions of bupivacaine. The potential risk from bupivacaine toxicity could also be reduced, without affecting analgesia, by combining a lower concentration of bupivacaine with fentanyl or sufentanil. Caution must also be exercised with the use of local anesthetic/narcotic solutions in prolonged epidural infusions because the pharmacokinetic variables of these solutions in children are also unknown. Until future studies are performed to evaluate the pharmacokinetics of these types of infusions into the caudal epidural space, we strongly urge close monitoring of mental status and the electrocardiogram during the infusion for signs and symptoms of central nervous system or cardiovascular toxicity. Consideration should also be given to monitoring serum levels of bupivacaine if these infusions are used on a routine basis. Furthermore, the pharmacokinetic data from the Richter et al. (16) study would suggest limiting the infusion of bupivacaine via the caudal epidural space to <48 h.

References

1. Yaster M, Maxwell L. Pediatric regional anesthesia. Anesthesiology 1989;70:324–38.
2. Dalens B. Regional anesthesia in children. Anesth Analg 1989;68:654–720.
3. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. Anesthesiology 1987;66:832–4.
4. Rice LJ, Pudimat MA, Hannallah RS. Timing of caudal block placement in relation to surgery does not affect duration of postoperative analgesia in paediatric ambulatory patients. Can J Anaesth 1990;37:429–31.
5. Broadman LM, Hannallah RS, Norden JM, McGill WA. "Kiddie caudals" experience with 1154 consecutive cases without complications (abstract). Anesth Analg 1987;66:S18.
6. Covino BG. Pharmacology of local anaesthetic agents. Br J Anaesth 1986;58:701–16.
7. Wolf AR, Valley RD, Fear DW, Roy WL, Lerman J. Bupivacaine for caudal analgesia in infants and children: the optimum effective concentration. Anesthesiology 1988;69:102–6.
8. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology 1988;68:387–91.
9. Eyres RL, Bishop W, Oppenheim RC, Brown TCK. Plasma bupivacaine concentrations in children during caudal epidural analgesia. Anaesth Intensive Care 1983;11:20–2.
10. Ecoffey C, Desparmet J, Berdeaux A, Maury M, Giudicelli JF, Saint-Maurice C. Bupivacaine in children: pharmacokinetics following caudal anesthesia. Anesthesiology 1985;63:447–8.
11. Desparmet J, Meistelman C, Barre J, Saint-Maurice C. Continuous epidural infusion of bupivacaine for postoperative pain relief in children. Anesthesiology 1987;67:108–10.
12. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988;69:261–4.
13. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. Br J Anaesth 1986;58:736–46.
14. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. Br J Anaesth 1986;58:732–5.
15. Jorfeldt L, Lofstrom B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on central circulation and respiration in man and dog. Acta Anaesthesiol Scand 1968;12:153–68.
16. Richter O, Klein K, Abel J, Ohnesorge FK, Wust HJ, Thiessen FMM. The kinetics of bupivacaine (Carbostesin) plasma concentrations during epidural anesthesia following intraoperative bolus injection and subsequent continuous infusion. Int J Clin Pharmacol Ther Toxicol 1984;22:611–7.
17. Van Kleef JW, Burm AGL, Vletter AA. Single-dose intrapleural versus intercostal blockade: nerve block characteristics and plasma concentration profiles after administration of 0.5% bupivacaine with epinephrine. Anesth Analg 1990;70:484–8.
18. Covino BG, Vassallo HG. Pharmacokinetic aspects of local anesthetic agents. In: Local anesthetics: mechanisms of action and clinical use. New York: Grune & Stratton, 1976:95–121.

Succinylcholine-Induced Hyperkalemic Arrest in a Patient With Severe Metabolic Acidosis and Exsanguinating Hemorrhage

David E. Schwartz, MD, Brian Kelly, MD, James E. Caldwell, MBChB, FFARCS, A. Sue Carlisle, PhD, MD, and Neal H. Cohen, MD, MPH, MS, FCCM

Departments of Anesthesia and Medicine, Division of Critical Care Medicine, University of California, San Francisco, School of Medicine, San Francisco, California

The administration of succinylcholine in normal humans results in a small increase in serum K^+ concentration (1,2). Depolarizing muscle relaxants act at the motor end plate of normal muscle cells and open a ligand-gated ion channel, allowing Na^+ and Ca^{2+} influx and K^+ efflux. This initiates depolarization of the muscle cell (2). Weintraub and colleagues (3) found that 100 mg of succinylcholine administered intravenously to anesthetized normal patients results in an average peak increase in serum K^+ concentration of 0.55 mEq/L. Uremic patients have a comparable increase in K^+ concentration when given a depolarizing muscle relaxant (4–6). Administration of succinylcholine to patients with a variety of other clinical conditions can produce an exaggerated hyperkalemic response, resulting in ventricular arrhythmias and cardiac arrest. This exaggerated release of K^+ after administration of succinylcholine has been reported in patients after massive trauma (7–9), burns (10–12), neuromuscular disease (13–17), intraabdominal infections (18), closed head injury (19), and near drowning (20). Patients with these clinical findings are believed to be "supersensitive" to the effects of succinylcholine (2). We describe a patient with severe acidemia and hypovolemic hypotension due to postpartum hemorrhage, without other known risk factors for hyperkalemia, who received succinylcholine to facilitate emergent intubation and suffered a hyperkalemic cardiac arrest.

Case Report

A 42-yr-old gravida 2, para 1 woman presented at 38-wk gestational age with ruptured membranes for cesarean section. She had no history of renal dysfunction or electrolyte disorders, and the remainder of her past medical history was unremarkable. The hematocrit was 33.5%. No other preoperative laboratory data were obtained. The patient underwent elective cesarean section under lidocaine epidural anesthesia. The procedure was uncomplicated. Estimated blood loss was 1000 mL.

At the time of admission to the obstetric recovery room, her arterial blood pressure was 100/70 mm Hg, and the heart rate was 120 beats/min. Oxygen saturation measured by pulse oximeter (Spo_2) was 98%.

Three hours postoperatively the patient complained of severe shoulder pain. The arterial blood pressure was 100/80 mm Hg, heart rate 150 beats/min, and Spo_2 94%. Within a few minutes, the patient became lethargic, and arterial blood pressure had decreased to 80 mm Hg systolic. A pulse oximeter signal could not be obtained. The hematocrit was 19%. No other laboratory data were obtained at this time. The patient was treated with rapid intravenous administration of crystalloid solutions while awaiting type-specific blood. Quickly thereafter the patient became unresponsive, and to ensure adequate gas exchange, bag-valve-mask ventilation was initiated. Despite manipulation of the airway, chest expansion was inadequate. Direct laryngoscopy was attempted without muscle relaxants; however, tense muscle tone prevented intubation. Succinylcholine (100 mg IV) was administered to facilitate laryngoscopy. The trachea was then intubated without difficulty and the lungs ventilated with 100% oxygen.

At the time of intubation an electrocardiographic (ECG) monitor was applied. The initial tracing showed a sinus tachycardia with a heart rate of 135 beats/min. Within 1 min of the administration of succinylcholine, peaked T waves were noted and the QRS complex was then observed to widen acutely. The rhythm degenerated into a polymorphic ventricular tachycardia followed by a sine wave pattern. The

Accepted for publication March 11, 1992.

Address correspondence to Dr. Schwartz, Department of Anesthesia, Division of Critical Care Medicine, University of California, San Francisco, 505 Parnassus, San Francisco, CA 94143-0624.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

patient became pulseless. Advanced cardiac life support was begun. Infusions of type-specific blood and crystalloid solution were administered. No blood products or bicarbonate were administered before the observed ECG changes. The initial postintubation arterial blood gas analysis obtained approximately 10 min after the beginning of advanced cardiac life support revealed pH 7.32, $Paco_2$ 10 mm Hg, Pao_2 337 mm Hg, HCO_3 5 mEq/L, and base excess −17 mEq/L; serum K^+ concentration was 8.2 mEq/L.

Despite vigorous therapy for hypovolemia and hyperkalemia, a cardiac rhythm could not be established, and the patient died approximately 45 min after initiation of advanced cardiac life support. Postmortem examination showed a large laceration in the posterior wall of the uterus with >1500 mL of intra-abdominal blood.

Discussion

The hyperkalemic response to succinylcholine administration is well described. A number of reports in the literature document the occurrence of hyperkalemia after administration of succinylcholine to patients with burns, massive tissue trauma, or neurologic disorders involving motor deficits (2,7–17). In some of these conditions, the mechanism of the exaggerated response to succinylcholine is the development of acetylcholine receptors in extrajunctional areas of the muscle cell (2). In patients with these conditions, the hyperkalemia resulting from administration of succinylcholine can cause cardiac arrest (2,12,15).

Roth and Wuthrich (15) suggest that succinylcholine is contraindicated in patients with renal failure, because of the occurrence of cardiac arrest in two uremic patients after succinylcholine administration. A number of investigators have subsequently shown that the administration of succinylcholine to uremic patients does not lead to an exaggerated release of K^+ (4–6). However, cardiac arrests can occur in patients with renal failure who receive succinylcholine, because they are hyperkalemic before the administration of a depolarizing muscle relaxant. The average increase in serum K^+ concentration of 0.5 mEq/L in these already hyperkalemic patients may be enough to induce ventricular arrhythmias.

No similar concern has been expressed about the use of succinylcholine in acidemic patients. Changes in the concentration of hydrogen ions have important effects on the serum K^+ concentration (21,22). In both humans (21) and animals (22), acidosis increases and alkalosis decreases the serum K^+ concentration. Changes in serum K^+ concentration are related only to changes in pH and are independent of alterations in Pco_2 or bicarbonate concentration (22). These changes also occur independently of alterations in total body stores of K^+ (21). On average, for every 0.1-unit change in extracellular pH, there is an inverse change of 0.6 mEq/L in the serum K^+ concentration (21). Thus, if a patient's arterial pH decreased from 7.40 to 7.00, there would be an increase in the serum K^+ concentration of approximately 2.4 mEq/L.

In the patient presented here we suggest that a likely explanation for the observed ECG changes and the subsequent cardiac arrest was severe hyperkalemia that developed after administration of succinylcholine to an already acidemic, hypovolemic, and hyperkalemic patient. Although arterial blood gas and electrolyte values obtained before cardiac arrest are not available, the most likely explanation for the timing of the ECG changes is hyperkalemia. The ECG changes observed by the physicians who were caring for the patient during the cardiac arrest are characteristic of hyperkalemia (23).

Based on the pH and the $Paco_2$ values of arterial blood gas obtained from the patient after endotracheal intubation, the pH before intubation and positive pressure ventilation was approximately 7.00. This pH change alone would increase a normal K^+ concentration of 4.5 mEq/L to approximately 6.9 mEq/L. The combination of the underlying acidemia and the anticipated rise in K^+ associated with succinylcholine administration resulted in severe hyperkalemia. This led to ventricular tachycardia and cardiac arrest in this already hypovolemic, hypotensive patient. Other causes for the hyperkalemia and associated ECG changes, such as renal dysfunction or an undiagnosed neurologic disorder, are unlikely.

This is the first report of a possible succinylcholine-induced hyperkalemic arrest in a patient whose only risk factor was severe acidemia. This case emphasizes the importance of considering acid-base status when administering depolarizing muscle relaxants, because in an acidemic patient the serum K^+ concentration may be elevated to dangerous levels before administration of succinylcholine. Although we do not suggest that succinylcholine is contraindicated in patients who are acidemic or that it results in an "exaggerated" release of K^+ in acidemic patients, we do believe that the clinician must consider underlying acid-base status before administration of a depolarizing muscle relaxant.

In acidemic patients, therapeutic maneuvers should be instituted to attempt correction of the acidemia before the administration of succinylcholine. Hyperventilation by bag and mask, as was attempted in our patient, may help to compensate for a metabolic acidosis and thus lower the serum K^+ concentration before administration of succinylcholine. The administration of sodium bicarbonate, although controversial for the treatment of lactic acidosis (24), is standard initial therapy for hyperkalemia.

The use of nondepolarizing muscle relaxants instead of succinylcholine should also be considered to facilitate the airway management of potentially hyperkalemic patients. Because nondepolarizing muscle relaxants do not cause elevated levels of serum K^+, their administration is unlikely to result in a dangerous elevation in serum K^+ concentration. However, in conventional doses, these drugs have a slower onset time than succinylcholine, which delays the attainment of adequate muscle relaxation to facilitate endotracheal intubation. The clinician must use his or her judgment and knowledge of the different effects of the various drugs when choosing a muscle relaxant for use in an acidemic, hyperkalemic patient who requires emergency endotracheal intubation.

References

1. Paton WDM. The effects of muscle relaxants other than muscular relaxation. Anesthesiology 1959;20:453–63.
2. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.
3. Weintraub HD, Heisterkamp DV, Cooperman LH. Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. Br J Anaesth 1969;41:1048–52.
4. Koide M, Waud BE. Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 1972;36:142–5.
5. Walton JD, Farman JV. Suxamethonium, potassium and renal failure. Anaesthesia 1973;28:626–30.
6. Miller RD, Way WL, Hamilton WK, Layzer RB. Succinylcholine induced hyperkalemia in patients with renal failure. Anesthesiology 1972;36:138–41.
7. Mazze RI, Escue HM, Houston JB. Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 1969;31:540–7.
8. Birch AA, Mitchell GD, Playford GA, Lang CA. Changes in serum potassium response to succinylcholine following trauma. JAMA 1969;210:490–3.
9. Kopriva C, Ratliff J, Fletcher JR, Van Tassel P, Stout R. Serum potassium changes after succinylcholine in patients with acute massive muscle trauma. Anesthesiology 1971;34:246–9.
10. Belin RP, Karleen CI. Cardiac arrest in the burned patient following succinylcholine administration. Anesthesiology 1966;27:516–8.
11. Schaner PJ, Brown RL, Kirksey TD, Gunther RC, Ritchey CR, Gronert GA. Succinylcholine-induced hyperkalemia in burned patients—1. Anesth Analg 1969;48:764–70.
12. Tolmie JD, Joyce TH, Mitchell GD. Succinylcholine danger in the burned patient. Anesthesiology 1967;28:467–70.
13. Cooperman LH, Strobel GE, Kennell EM. Massive hyperkalemia after administration of succinylcholine. Anesthesiology 1970;32:161–4.
14. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 1970;213:1867–71.
15. Roth F, Wuthrich H. The clinical importance of hyperkalemia following suxamethonium administration. Br J Anaesth 1969; 41:311–5.
16. Gravlee GP. Succinylcholine-induced hyperkalemia in a patient with Parkinson's disease. Anesth Analg 1980;59:444–6.
17. Feldman JM. Cardiac arrest after succinylcholine administration in a pregnant patient recovered from Guillain-Barré syndrome. Anesthesiology 1990;72:942–4.
18. Kohlschutter B, Baur H, Roth F. Suxamethonium-induced hyperkalemia in patients with severe intra-abdominal infections. Br J Anaesth 1976;48:557–61.
19. Stevenson PH, Birch AA. Succinylcholine-induced hyperkalemia in a patient with a closed head injury. Anesthesiology 1979;51:89–90.
20. Tong TK. Succinylcholine-induced hyperkalemia in near-drowning. Anesthesiology 1987;66:720.
21. Burnell JM, Villamil MF, Uyeno BT, Scribner BH. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. J Clin Invest 1956;35:935–9.
22. Simmons DH, Avedon M. Acid-base alterations and plasma potassium concentration. Am J Physiol 1959;197:319–26.
23. Fisch C. Electrocardiography and vectorcardiography. In: Braunwald E, ed. Heart disease: A textbook of cardiovascular medicine. 3rd ed. Philadelphia: WB Saunders, 1988:215–6.
24. Stacpoole PW. Lactic acidosis: the case against bicarbonate therapy. Ann Intern Med 1986;105:276–9.

Succinylcholine-Induced Hyperkalemia 8 Weeks After a Brief Paraplegic Episode

James W. Greenawalt III, MD

Department of Anesthesiology, Saint Francis Hospital, Tulsa, Oklahoma

Succinylcholine-induced hyperkalemia has been well described in a variety of neuromuscular pathologic states. Recent thermal injury, spinal cord trauma with paresis, prolonged immobility, primary neuromuscular disease, abdominal sepsis, and recent stroke are thought by many to contraindicate the use of succinylcholine. A neurologically normal patient manifested a succinylcholine-induced hyperkalemic cardiac arrest 2 mo after transient paraplegia that developed after surgical repair of a transected thoracic aorta. Even transient paraplegia may contraindicate the routine use of depolarizing neuromuscular blocking drugs.

Case Report

A 26-yr-old, 70-kg man was scheduled for removal of a femoral Klemm nail. Past medical history was significant for a successful repair of a transected descending thoracic aorta after a motor vehicle accident 2 mo earlier. After this operation, the patient manifested a transient lower extremity paraplegia that resolved over the next 4–6 h postoperatively and a permanent left recurrent laryngeal nerve palsy. His right femur fracture was initially managed with traction and bed rest. On the sixth postoperative day, he underwent uneventful internal fixation of the fracture with a Klemm nail. Succinylcholine was used to facilitate orotracheal intubation for both these operations without incident. The patient was walking without assistance at discharge from the hospital 10 days after admission.

The patient continued to walk without assistance at home after discharge. He related being "weak," but he was able to climb stairs and get in and out of a car unassisted. His physical examination was unremarkable, as was his hemogram. Just before induction of anesthesia, his arterial blood pressure was 160/90 mm Hg, and his heart rate was 105 beats/min.

Oxygen by face mask and gallamine (20 mg IV) were administered. Three minutes later, thiopental (280 mg IV) and succinylcholine (100 mg IV) were administered. After hyperventilation with oxygen, the patient was orotracheally intubated 2 min later without obvious muscle fasciculations. Seconds after intubation, electrocardiographic (ECG) lead II revealed bigeminal premature ventricular contractions. The pulse oximeter indicated an oxygen saturation of 100%. The patient was then hyperventilated with 70% nitrous oxide with oxygen and 3.5% isoflurane, and lidocaine (100 mg IV) was administered. The ST segments rapidly elevated. The ECG complex became sinusoidal in appearance over the next 3 min. The heart rate was 100 beats/min. Six minutes after thiopental and succinylcholine administration, the arterial blood pressure was 75/53 mm Hg. Over the next 60 s, the patient became profusely diaphoretic, his skin color became ashen gray, his carotid pulse was barely palpable, and no blood pressure could be obtained. The nitrous oxide and isoflurane were discontinued, and the lungs were ventilated with oxygen. A capnogram revealed that the end-tidal carbon dioxide pressure had decreased from 30 to 17 mm Hg. The defibrillator malfunctioned, and closed-chest cardiac compressions were begun for 2 min, after which the ECG and vital signs returned to normal. The operation was postponed, and an arterial line was inserted. Some 11–12 min after the succinylcholine was administered, a clinically nonhemolyzed sample of arterial blood revealed a serum potassium concentration of 6.9 mEq/L. The patient was transported to the postanesthesia care unit and made an uneventful recovery. Thirty minutes later, the serum potassium level was 3.6 mEq/L.

Discussion

It is unlikely the hyperkalemia seen in this case was due to hemolysis because the sample was obtained from a 20-gauge radial artery. Furthermore, the lab-

Accepted for publication April 17, 1992.

Address correspondence to Dr. Greenawalt, 6839 South Canton, Tulsa, OK 74136.

©1992 by the International Anesthesia Research Society

0003-2999/92/$5.00

oratory did not report any evidence of hemolysis. Massive muscle trauma can cause hyperkalemia, but the trauma was sufficiently remote in this case, making this etiology unlikely. Closed-chest cardiopulmonary resuscitation could have elevated the serum potassium level, but the temporal association of the administration of the succinylcholine and the development of the ECG findings with cardiovascular collapse impute succinylcholine as the agent responsible for the hyperkalemia. The serum potassium levels of 6.9 mEq/L 12 min after succinylcholine administration and 3.6 mEq/L 30 min later are in agreement with the potassium efflux described by Gronert and Theye (1).

Succinylcholine-induced hyperkalemia is a well-known phenomenon associated with certain pathologic states. Burns (2), neuromuscular diseases (3), renal failure (4), severe intraabdominal infections (5), closed head trauma (6), and prolonged disuse (7,8) can all cause laboratory and clinical evidence of hyperkalemia shortly after the administration of a depolarizing neuromuscular blocking drug or acetylcholine. Numerous reports (9,10) attest to the danger associated with the use of depolarizing neuromuscular blocking drugs in patients with spinal cord trauma. When succinylcholine-induced hyperkalemia associated with upper and lower motor neuron pathology is reported, it is associated with an identifiable paresis of some or all of the extremities (3,9,10). The current report is believed to be unique in that the patient was fully ambulatory and without a focal neurologic deficit.

The administration of a nondepolarizing muscle relaxant before the administration of a depolarizing drug attenuates but does not ablate the hypersensitivity response described in denervated muscle (1). Despite the complete absence of fasciculations in our patient, he still manifested hyperkalemia of sufficient magnitude to cause cardiovascular collapse.

When succinylcholine or acetylcholine is applied to muscle or to the end plate of an intact lower motor neuron unit, only the end plate depolarizes. Ten to 14 days after denervation (11,12), and after a similar period of disuse (8), the entire muscle begins to act like an end plate when acetylcholine or succinylcholine is applied to it (1). In denervated muscle, succinylcholine and acetylcholine depolarize the entire muscle membrane, and permeability increases dramatically, liberating 20 times the potassium that normal muscle liberates. This membrane hypersensitivity may last 6–12 mo and perhaps longer if the disease process is progressive (3). Muscle atrophied by disuse produces similar but less exaggerated effluxes of potassium (1).

Although this patient was neither paraplegic nor bedfast, he manifested a response similar in magnitude to those patients with muscular denervation and resultant end-plate proliferation. A brief period of upper or lower motor neuron dysfunction, coupled with only mild disuse, may be sufficient to initiate and maintain the proliferation of motor end plates with the attendant hypersensitivity response to depolarization.

Although a direct cause-and-effect relation between succinylcholine and the hyperkalemic cardiovascular collapse observed in this patient has not been absolutely conclusive, the temporal sequence of events observed in this patient points strongly toward a cause and effect. This case report suggests that caution should be used when administering depolarizing neuromuscular relaxants to patients who have apparently recovered from a recent upper or lower motor neuron disease process. Further, the administration of a low-dose nondepolarizing drug before a depolarizing drug may not prevent the hyperkalemic response seen with the use of depolarizing drugs in these patients. The absence of focal neurologic deficits or significant muscular "disuse" atrophy does not ensure a "normal" response to a depolarizing muscular relaxant in similar patients.

References

1. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.
2. Schaner PJ, Brown RL, Kirksey TD, et al. Succinylcholine-induced hyperkalemia in burned patients—1. Anesth Anal 1969;48:764–70.
3. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 1970;213:1867–71.
4. Powell JN. Suxamethonium-induced hyperkalaemia in a uremic patient. Br J Anaesth 1970;42:804–6.
5. Kohlschutter B, Baur H, Roth F. Suxamethonium-induced hyperkalemia in patients with severe intra-abdominal infections. Br J Anaesth 1976;48:557–62.
6. Stevenson PH, Birch AA. Succinylcholine-induced hyperkalemia in a patient with a closed head injury. Anesthesiology 1979;51:89–90.
7. Gronert GA, Theye RA. Effect of succinylcholine on skeletal muscle with immobilization atrophy. Anesthesiology 1974;40: 268–71.
8. Solandt DY, Partridge RC, Hunter J. The effect of skeletal fixation on skeletal muscle. J Neurophysiol 1943;6:17–22.
9. Stone WA, Beach TP, Hamelberg W. Succinylcholine—danger in the spinal-chord-injured patient. Anesthesiology 1970;32: 168–9.
10. Tobey RE. Paraplegia, succinylcholine and cardiac arrest. Anesthesiology 1970;32:359–64.
11. Thesleff S. Effects of motor innervation on the chemical sensitivity of skeletal muscle. Physiol Rev 1961;40:734–42.
12. Gronert GA, Lambert EH, Theye RA. The response of denervated skeletal muscle to succinylcholine. Anesthesiology 1973; 39:13–22.

Vertebral Artery Pseudoaneurysm: A Rare Complication of Internal Jugular Vein Catheterization

Hiroshi Aoki, MD, Toshiki Mizobe, PhD, MD, Shinnji Nozuchi, MD, Tetsuo Hatanaka, MD, and Yoshifumi Tanaka, PhD, MD

Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Percutaneous catheterization of the internal jugular vein is widely practiced for central venous access and flow-directed pulmonary artery catheter placement. This approach has many well-known advantages over the subclavian route (1). It also has the potential for several critical complications, especially accidental arterial puncture. We report a case of vertebral artery pseudoaneurysm caused by internal jugular vein puncture.

Case Report

A 72-yr-old man entered the hospital because of acute exacerbation of chronic obstructive pulmonary disease of 30-yr duration. On admission, analysis of arterial blood gases revealed pHa 7.42, Pao_2 35.8 mm Hg, $Paco_2$ 63.9 mm Hg, and a base excess of −12.4 mEq/L while the patient was breathing room air, indicating the terminal stages of pulmonary insufficiency. On the following day, the patient developed circulatory shock with respiratory arrest and required cardiopulmonary resuscitation. To obtain central venous access, catheterization was attempted through the right internal jugular vein into the superior vena cava. Because arterial blood was aspirated on the first attempt with a 22-gauge needle, manual compression was begun, and the catheter was placed through the right femoral vein. That night, a hematoma was observed in the right neck region, along with a decrease in arterial blood pressure and hematocrit, requiring blood transfusion. The hematoma gradually enlarged over several days to the right scapular region, but conservative therapy was continued.

On the 70th day, the patient complained of pain and numbness in the right shoulder extending to the forearm, suggesting compression of the brachial plexus by the hematoma. A computed tomography scan of the neck demonstrated a giant hematoma and compression of the internal jugular vein and trachea (Figure 1). Surgical removal of the hematoma was believed to be high risk in view of the severity of the pulmonary insufficiency (Pao_2 40–80 mm Hg; $Paco_2$ 50–90 mm Hg; inspired O_2 concentration [FIo_2] 0.35–0.5, assisted by a respirator and synchronized intermittent mandatory ventilation mode) and the need for resuscitation several times. Digital subtraction angiography performed on the 104th day revealed a pseudoaneurysm, probably fed from the vertebral artery (Figure 2). Because the possibility of rupture was thought to be high, we believed that a surgical procedure was necessary despite the patient's poor general condition. The cardiovascular surgery staff was consulted, but the patient developed circulatory shock with a decrease in hematocrit. Rupture of the pseudoaneurysm was suspected, and an emergency operation was therefore performed.

When the pseudoaneurysm was opened and the hematoma removed, a jet of arterial blood was observed from a hole with a diameter of approximately 1 mm in the right vertebral artery. After clamping of the right subclavian artery, the site of hemorrhage was sutured and the operation completed (Figure 3). The procedure was relatively uncomplicated. The patient's general condition remained relatively stable in the intensive care unit using a respirator and catecholamines (Pao_2 70–125 mm Hg; $Paco_2$ 40–80 mm Hg; FIo_2 0.3–0.4), but his pulmonary insufficiency was exacerbated suddenly on the 11th postoperative day, and the patient died despite attempts at cardiopulmonary resuscitation.

Discussion

Although the method of internal jugular vein catheterization introduced by English et al. (2) and Jernigan et al. (3) was thought to have few complications, various complications have been reported, including pneumo-, hydro-, and hemothorax caused by puncture of the pleura (4,5); chylothorax as the result of

Accepted for publication March 31, 1992.

Address correspondence to Dr. Aoki, Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamikyo-Ku, Kyoto 602, Japan.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

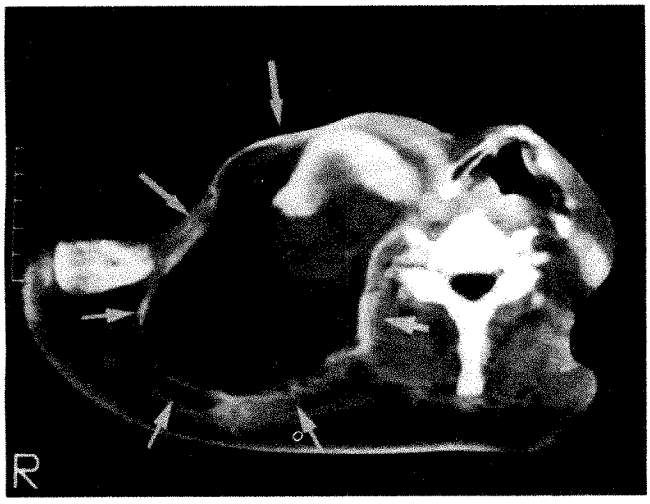


Figure 1. Computed tomography scan of the neck showing giant hematoma (*arrows*) and compression of the internal jugular vein (enhanced) and trachea.

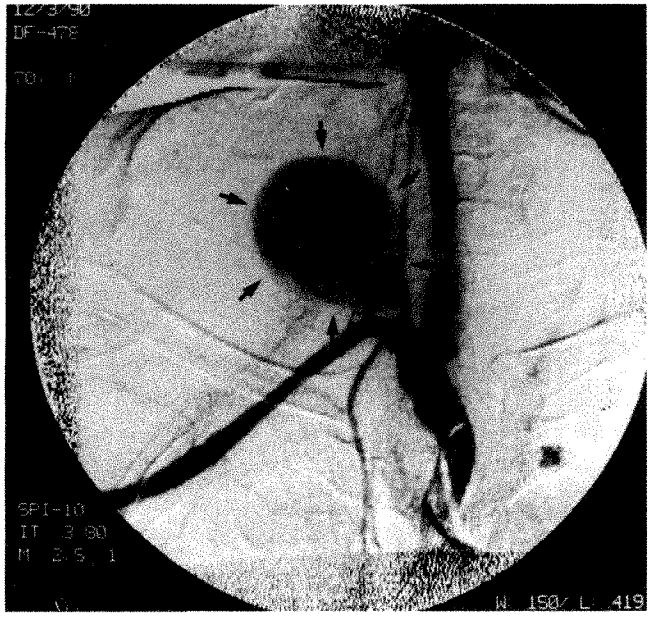


Figure 2. Digital subtraction angiography showing pseudoaneurysm (*arrows*) fed from the vertebral artery.



Figure 3. Photograph taken during the operation. The point of hemorrhage has been sutured (*arrow*) after removal of blood clot in the pseudoaneurysm.

thoracic duct injury (6); Horner's syndrome, probably caused by compression by hematoma or direct needle injury (7); and hematoma at the puncture site (8). A case of fistula formation between the inferior thyroid artery and internal jugular vein (9) and a case of puncture of the ascending cervical artery (10) have also been reported. Because there are many arteries and veins in the neck region, undetected injuries of these vessels may occasionally occur. Moreover, because the vertebral artery is surrounded by a very rich network of veins, there are several reports of vertebral arteriovenous fistula (11–13). Most of these cases occurred after heart surgery with extracorporeal circulation; that is, systemic heparinization was performed after accidental injuries of arteries and probably caused and aggravated such complications.

Amaral et al. (14) reported a case of vertebral artery pseudoaneurysm as a complication of subclavian vein catheterization. That case was described in a female patient who received total knee replacement because of an infected knee prosthesis. She seemed to have no hemorrhagic tendency. There was no evidence of disseminated intravascular coagulation, and systemic heparinization was never performed. Nevertheless, this hematoma occurred. Our patient also had no lack of capacity for hemostasis. These two cases suggest the possibility of complications with injury of the arteries, even in those with normal hemostasis and those who undergo common operations without systemic heparinization. The reason for this seems to be the anatomic construction of the vertebral artery. The vertebral artery arises as the first branch of the subclavian artery and courses cephalad between the

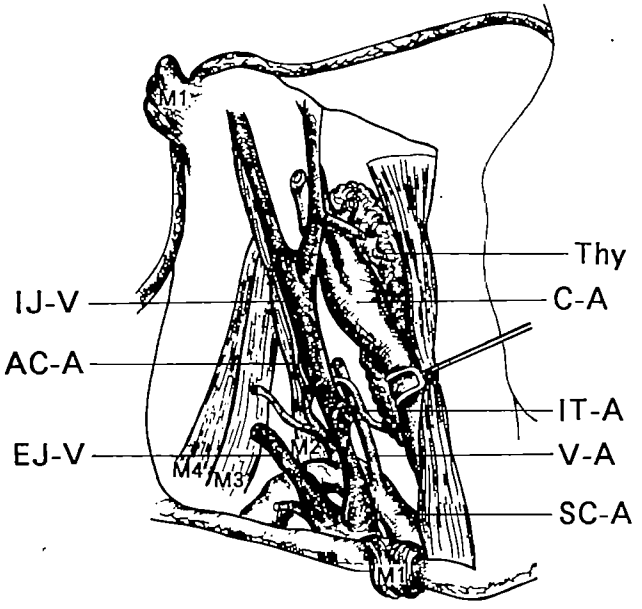


Figure 4. The anatomy of the neck region. IJ-V, internal jugular vein; EJ-V, external jugular vein; C-A, common carotid artery; V-A, vertebral artery; SC-A, subclavian artery; IT-A, inferior thyroid artery; AC-A, ascending cervical artery; M1, sternocleidomastoid muscle; M2, anterior scalene muscle; M3, medial scalene muscle; M4, posterior scalene muscle; Thy, thyroid gland. (Reprinted with permission from von Kahle W, Leonhardt H, Platzer W. Taschenatlas der Anatomie. Stuttgart: Georg Thieme Verlag, 1979, page 181, with some modifications.)

longus colli medially and the anterior scalene muscle laterally, following its ascent through the foramina of the transverse processes of C-6 to C-1. This extraspinous portion of the artery, approximately 4 cm, lies deeper than other vessels, and hemostasis is difficult to achieve by manual compression. The anatomy in this region of the neck is shown in Figure 4. The vertebral artery (V-A) lies slightly more medially and deeper than the internal jugular vein (IJ-V). Moreover, the internal jugular vein is also located adjacent to the common carotid artery (C-A) and crosses under the inferior thyroid artery (IT-A). The ascending cervical artery (AC-A) is often a branch of the inferior thyroid artery, with the junction situated on the anterior scalene muscle (M2) and beneath the internal jugular vein. Therefore, accidental injuries of these vessels may occur during attempts at internal jugular vein cannulation in the wrong direction and at the wrong depth. In our case, although puncture was of course performed by a well-trained operator, conditions were not favorable because it was performed during external chest compression. Therefore, the needle is thought to have been shifted slightly inward and deeper, resulting in the puncture of the vertebral artery. To avoid this complication, care should be taken not to insert the needle too deeply or penetrate the internal jugular vein. Moreover, it is important to exert sufficient manual compression on the puncture site to prevent serious complications at an early stage; however, the fact must be kept in mind that hemostasis by manual compression is anatomically difficult to achieve, as mentioned previously. In addition, because pseudoaneurysm differs from true aneurysm in that it lacks a specific three-layer structure (15), it enlarges progressively when left untreated and finally leads to rupture, as in our case. Thus, when a puncture of one of the arteries is strongly suspected and a large hematoma is created, intensive follow-up care, such as radiographic examination, computed tomography scanning, and angiography, should ensue.

References

1. Defalque RJ. Percutaneous catheterization of the internal jugular vein. Anesth Analg 1974;53:116–21.
2. English ICW, Frew RM, Pigott JF, Zaki M. Percutaneous catheterisation of internal jugular vein. Anaesthesia 1969;24: 521–31.
3. Jernigan WR, Gardner WC, Mahr MM, Milburn JL. Use of the internal jugular vein for placement of central venous catheter. Surg Gynecol Obstet 1970;130:520–4.
4. McGoon MD, Benedetto PW, Greene BM. Complication of percutaneous central venous catheterization: a report of two cases and review of the literature. Johns Hopkins Med J 1979;145:1–6.
5. Hopkins RB, Parkin CE. Hydrohemothorax following percutaneous internal jugular vein cannulation recognized by intravenous pyelography. Anesth Analg 1978;57:507–11.
6. Khalil KG, Parker FB, Mukherjee N, Webb WR. Thoracic duct injury. A complication of jugular vein catheterization. JAMA 1972;221:908–9.
7. Parikh RK. Horner's syndrome. A complication of percutaneous catheterisation of internal jugular vein. Anaesthesia 1972; 27:327–9.
8. Brown CS, Wallace CT. Chronic hematoma—a complication of percutaneous catheterization of the internal jugular vein. Anesthesiology 1976;45:368–9.
9. Ortiz J, Dean WF, Zumbro GL, Treasure RL. Arteriovenous fistula as a complication of percutaneous internal jugular vein catheterization: case report. Milit Med 1976;141:171.
10. Wisheart JD, Hassan MA, Jackson JW. A complication of percutaneous cannulation of the internal jugular vein. Thorax 1972;27:496–9.
11. Piechowiak H, Buchels H, Ingrisch H, Hess H. AV-Fistel der arteria vertebralis: eine seltene Komplikation nach zentralvenoser Katheterisierung. Anaesthesist 1984;33:327–9.
12. Dodson T, Quindlen E, Crowell R, McEnany MT. Vertebral arteriovenous fistulas following insertion of central monitoring catheters. Surgery 1980;87:343–6.
13. Baleriaux-Waha D, Jeanmart L, Brihaye J, Henneaux J. Traumatic arteriovenous fistulas of the vertebral artery. Neuroradiology 1976;11:83–5.
14. Amaral JF, Grigoriev VE, Dorfman GS, Carney WI. Vertebral artery pseudoaneurysm. A rare complication of subclavian artery catheterization. Arch Surg 1990;125:546–7.
15. Titus JL, Kim H. Blood vessels and lymphatics. In: Kissane JM, ed. Anderson's pathology. 8th ed. St. Louis: Mosby, 1985:707.

Craniotomy in a Patient With Eisenmenger's Syndrome

Mark A. Chaney, MD

Department of Anesthesiology, Loyola University Medical Center, Foster G. McGaw Hospital, Maywood, Illinois

Eisenmenger's syndrome, as defined by Wood (1) in 1958, is the presence of high pulmonary vascular resistance associated with pulmonary hypertension at or close to systemic values, with a reversed or bidirectional shunt at the aortopulmonary, interventricular, or interatrial levels. The syndrome is rare. Death usually occurs in the third or fourth decade of life; survival to age 63 yr has been documented, but this is exceptional (2–5). The mainstay of therapy is heart-lung transplantation, and Eisenmenger's syndrome is currently the most common entity requiring this procedure (6–8). Most case reports of noncardiac operations in patients with Eisenmenger's syndrome involve obstetrics (9–17). The balance of case reports have detailed relatively minor procedures (18–23). Morbidity and mortality associated with all noncardiac operations in patients with Eisenmenger's syndrome remain very high (9–23). We describe here the first instance of the successful management of a patient with Eisenmenger's syndrome undergoing a craniotomy for a large temporoparietal abscess.

Case Report

The patient was a 36-yr-old man with a left temporoparietal abscess. Past medical history was significant for Eisenmenger's syndrome. His last cardiac catheterization, 11 yr before, revealed systemic pulmonary artery pressures. He had no other medical problems and denied any previous operations. Medications included theophylline, enalapril, digoxin, phenytoin, dexamethasone, and multiple antibiotics. Physical examination was remarkable for systolic and diastolic murmurs, clubbing, central cyanosis, Janeway lesions, and Wernicke's aphasia. He had polycythemia (hemoglobin 21.3 g/dL; hematocrit 63.1%) and thrombocytopenia (platelets 111,000/mm^3). A coagulation disorder was also discovered. The prothrombin time and partial thromboplastin time were increased (12.7/27.8 s), as was the bleeding time (>15 min). Fibrin split products were mildly increased, and fibrinogen and Factor VII levels were mildly decreased. With an F_{IO_2} of 0.2, pHa was 7.49, P_{aCO_2} 28 mm Hg, and P_{aO_2} 41 mm Hg (81% saturation). All blood cultures were negative.

An electrocardiogram revealed sinus rhythm, right-axis deviation, right ventricular hypertrophy, incomplete right bundle branch block, and nonspecific ST segment changes. Chest radiograph showed the heart size to be normal, but the pulmonary artery segments were "enormous." There were no infiltrates. Transthoracic echocardiography (two-dimensional, M-mode, Doppler) revealed a large ventricular septal defect (>2 cm) with a bidirectional shunt. The great vessel orientation was normal. Right ventricular hypertrophy, marked right ventricular enlargement, and marked right atrial enlargement were present. In contrast, the left ventricular size was normal. Severe pulmonary hypertension with pulmonic regurgitation was documented. The aortic, mitral, and tricuspid valves were normal. Magnetic resonance imaging revealed a large left temporoparietal abscess (5-cm diameter) with accompanying mass effect and edema.

A consultant hematologist believed that the coagulation defects were secondary to a low-grade disseminated intravascular coagulation, coupled with vitamin K deficiency. Therapy with cryoprecipitate, platelets, and phlebotomy before surgery was recommended. After these interventions, the hematocrit and coagulation tests returned to normal values.

All medications were continued on the morning of surgery. No preoperative sedation was given. A right subclavian single-lumen catheter had been placed by the surgical service the night before. All intravenous lines were meticulously deaired. Additional monitoring included a right radial 20-gauge arterial line, central venous pressure measurements from the right subclavian line, a precordial Doppler probe, and a Foley catheter. A pulmonary artery catheter was not inserted. Preinduction hemodynamics were arterial blood pressure 140/60 mm Hg (mean 110), heart rate 70 beats/min (sinus rhythm), and central venous pressure 18 mm Hg. Oxygen saturation was 85% while breathing room air. Induction of anesthesia

Accepted for publication April 10, 1992.

Address correspondence to Dr. Chaney, Loyola University Medical Center, Foster G. McGaw Hospital, Department of Anesthesiology, 2160 South First Avenue, Maywood, IL 60153.

©1992 by the International Anesthesia Research Society
0003-2999/92/$5.00

was accomplished with a high-dose narcotic technique. Fentanyl and midazolam were administered slowly while the patient spontaneously breathed 100% oxygen. Once consciousness was lost and controlled ventilation through a mask proved easy, vecuronium was administered intravenously for muscle relaxation. Before laryngoscopy, 100 μg/kg of fentanyl and 6 mg of midazolam had been administered intravenously with essentially no change in hemodynamics. Oxygen saturation at this time had increased to 97%. Laryngoscopy and tracheal intubation were then performed easily without hemodynamic change. Mechanical ventilation was initiated with a tidal volume of 10 mL/kg and at a rate to maintain hyperventilation. After tracheal intubation with an F_{IO_2} of 1.0, pHa was 7.53, P_{aCO_2} 25 mm Hg, and P_{aO_2} 159 mm Hg. A transesophageal echocardiography probe was then placed easily, and verification of the preoperative transthoracic echocardiography report was documented. The probe was then removed. The supine position was maintained throughout the procedure, with the head turned to the right.

Hemodynamics remained unchanged during initial surgical incision and craniotomy. The first 2 h of the operation were uneventful. During this time, oxygen saturation was extremely sensitive to changes in mean arterial pressure and central venous pressure. As long as the mean arterial pressure was >90 mm Hg and the central venous pressure was >16 mm Hg, the oxygen saturation remained between 95% and 100%. If allowed to decrease below these values, oxygen saturation decreased precipitously to 70%–80%. During the first 2 h of the operation, there was very little ongoing blood loss, so that intravascular volume was maintained with intravenous crystalloid administration.

Approximately 2.5 h into the procedure, blood loss occurred fairly rapidly. At this time, the mean arterial pressure decreased to 70 mm Hg, and the central venous pressure decreased to 12 mm Hg. The heart rate increased to 110 beats/min, maintaining sinus rhythm. With an F_{IO_2} of 1.0, pHa was 7.45, P_{aCO_2} 30 mm Hg, P_{aO_2} 41 mm Hg, and hematocrit 27% (starting hematocrit was 40%). Rapid administration of packed red blood cells over the next hour restored hemodynamics to preinduction values with significant improvement in arterial blood gases. A total of 7 U of packed red blood cells was administered along with supplemental platelets, fresh-frozen plasma, and cryoprecipitate. At no time were vasoactive medications required. Hemostasis was eventually secured, and the operation proceeded without incident. Urine output was well maintained throughout the entire operation, which lasted just over 5 h. Continuous monitoring by precordial Doppler never revealed signs indicative of venous air embolism.

On arrival at the recovery area, hemodynamics were arterial blood pressure 140/80 mm Hg (mean 116), heart rate 72 beats/min (sinus rhythm), and central venous pressure 15 mm Hg. With an F_{IO_2} of 1.0, pHa was 7.38, P_{aCO_2} 37 mm Hg, P_{aO_2} 61 mm Hg, and hematocrit 48%. The patient did extremely well in the immediate postoperative period. Extubation of the trachea occurred on postoperative day 2 after tolerating weaning without difficulty. He retained full neurologic function and sustained a significant improvement in mental status.

Discussion

Of the few case reports concerning noncardiac surgery in patients with Eisenmenger's syndrome, most involve obstetrics. Mortality in these selected cases is high, approximately 30% for vaginal delivery and up to 75% for cesarean section (9–17). The balance of case reports have been concerned with relatively minor procedures (18–23). Morbidity and mortality associated with all noncardiac operations in patients with Eisenmenger's syndrome remains very high (9–23). Regional as well as general anesthesia has been utilized with varying degrees of success. Before administering anesthesia to a patient with Eisenmenger's syndrome, one must comprehend the pathophysiology involved and the unique complications that may develop (9,18,21–26). Of prime importance hemodynamically is control of shunt direction, maintenance of normovolemia, maintenance of a stable heart rate, and avoidance of myocardial depression. These patients are at risk for thromboemboli, paradoxic emboli, endocarditis, and arrhythmias. One must also decide whether or not to use a pulmonary artery catheter during management.

Shunt direction in Eisenmenger's syndrome is determined by the balance between the pulmonary and systemic vascular resistances (1,18,21,24,26). An increase in right-to-left shunting worsens cyanosis, and an increase in left-to-right shunting induces right ventricular failure. Most authorities believe that the pulmonary vascular resistance is fixed (high) from long-standing pulmonary hypertension (1,10, 18,21,24,26). There is some evidence, however, that the pulmonary vasculature remains reactive. Midwall et al. (11) found the pulmonary vasculature of a 28-yr-old parturient with Eisenmenger's syndrome to be reactive (i.e., vasodilate) to oxygen. Wong et al. (27) similarly showed in four patients with Eisenmenger's syndrome the ability of the pulmonary vasculature to vasodilate to nifedipine. Clinically, however, it is safe to assume that the pulmonary vascular resistance will be fixed. The systemic vasculature, in contrast, remains normally reactive. Thus, if systemic vascular resistance decreases, cyanosis

will occur (implies increased right-to-left shunting), and if systemic vascular resistance increases, right ventricular failure will ensue (implies increased left-to-right shunting). Epidural anesthesia with local anesthetics has been used successfully during management of these patients as long as initiation of sympathetic blockade was gradual and normovolemia was maintained (10,11,13,16,23). It is tempting to formulate an intraoperative plan where worsening cyanosis will be treated with vasoconstrictors. This has been done with mixed results. Case reports by Bird and Strunin (19) and Blake et al. (28) detail deterioration in patients given metaraminol and phenylephrine, respectively, whereas Skinner et al. (20) document improvement in a patient given phenylephrine. It is apparent that patients with Eisenmenger's syndrome do not respond in a predictable manner to vasoactive medications, and it is prudent to avoid their administration whenever possible, as we did in our patient. Increases in systemic vascular resistance due to surgical stimulation with associated increased sympathetic outflow, inducing right ventricular failure, was also one of our concerns. We chose a high-dose narcotic technique to establish a deep level of anesthesia to blunt sympathetic response to craniotomy without inducing myocardial depression.

Control of shunt direction in patients with Eisenmenger's syndrome is best accomplished by maintenance of normovolemia (18,21,23,24). Hypovolemia tends to increase right-to-left shunting, and hypervolemia tends to increase left-to-right shunting. Our patient was an excellent example of this concept. If the mean arterial and central venous blood pressures were allowed to decrease, desaturation quickly ensued, implying increased right-to-left shunting. During the period of rapid blood loss, significant desaturation occurred that resolved once normovolemia was reestablished. If strict attention is paid to maintenance of normovolemia, there will be no need to administer vasoactive medications that will have unpredictable effects.

Maintenance of a stable heart rate (sinus rhythm preferable) is also important, because bradycardia or tachycardia may cause unpredictable changes in shunt direction (19). Myocardial depression is also to be avoided. It is important to understand that in these patients it is the right ventricle, which must eject against an elevated pulmonary vascular resistance, and not the left ventricle that is at risk for failure (1,9).

Patients with Eisenmenger's syndrome are particularly susceptible to complications arising from emboli (9,10,17,23). Thromboemboli are perhaps the most common cause of morbidity and mortality and are formed in the vascular system as a consequence of polycythemia from long-standing cyanosis. Phlebotomy is frequently performed to reduce the risk of thromboembolism. Anticoagulation with heparin or coumadin is also an option. Polycythemia may also initiate disseminated intravascular coagulation. With such a significant risk for paradoxic emboli, meticulous deairing of access lines is mandatory (29). Theoretically, nitrous oxide should be avoided but has been utilized during management of these patients without untoward effects (18,19,21,22). Leaving the transesophageal echocardiography probe in place throughout the procedure as a monitor for venous air embolism and paradoxic air embolism was an option. We believed, however, that the precordial Doppler probe was sufficiently sensitive and that any venous air embolism detected in our patient would necessarily be considered paradoxic. We were also concerned about possible complications from prolonged use of the probe with the head turned laterally, because transient vocal cord paralysis under similar circumstances has been reported (30).

As is the case with other congenital heart defects, prophylactic antibiotics must be administered perioperatively to combat bacterial endocarditis (31).

Arrhythmias are frequently encountered during management, most commonly atrioventricular nodal block and bundle branch block, and are poorly tolerated (1).

A decision must be made concerning the use of a pulmonary artery catheter in the anesthetic management of a patient with Eisenmenger's syndrome. Some believe them to be necessary, and pulmonary artery catheters have been used in selected cases (9–11,15–17). It is this author's opinion, and one shared by others, that utilization of a pulmonary artery catheter in a patient with Eisenmenger's syndrome will garner little useful information and carries with it very significant risks, such as thrombosis with embolization, pulmonary artery rupture, and arrhythmia initiation (9,21,32–35). Indeed, Devitt et al. (17) details a case in which a patient with Eisenmenger's syndrome died immediately on attempted withdrawal of a pulmonary artery catheter on the fourth postoperative day. Permission for autopsy was denied, and the authors postulated that thrombosis with embolization was the probable cause of death. We believed that monitoring central venous pressure was sufficient, especially with the understanding that the right ventricle, not the left ventricle, was at risk for failure.

In summary, we present here the successful anesthetic management of a patient with Eisenmenger's syndrome secondary to a ventricular septal defect who underwent a craniotomy for removal of a large temporoparietal abscess. A complete understanding of the pathophysiology involved and the unique

complications that may develop is essential. Hemodynamically, of utmost importance is maintenance of normovolemia, prevention of right ventricular failure, and avoidance of vasoactive medications. Complications that may develop include thromboemboli, paradoxic emboli, endocarditis, and arrhythmias. With strict attention to detail, these very high-risk patients can be managed successfully during major noncardiac surgery.

References

1. Wood P. The Eisenmenger syndrome; or pulmonary hypertension with reversed central shunt. Br Med J (Clin Res) 1958;2: 701–9, 755–62.
2. Young D, Mark H. Fate of the patient with the Eisenmenger syndrome. Am J Cardiol 1971;28:658–69.
3. Gould L, Gopalaswamy C. Late survival of a patient with ventricular septal defect and Eisenmenger syndrome. Angiology 1982;33:769–75.
4. Warnes CA, Boger JE, Roberts WC. Eisenmenger ventricular septal defect with prolonged survival. Am J Cardiol 1984;54: 460–2.
5. McManus BM, Hahn PF, Smith JA, Roberts WC, Jackson JH. Eisenmenger ductus arteriosus with prolonged survival. Am J Cardiol 1984;54:462–4.
6. McGregor CGA, Jamieson SW, Baldwin JC, et al. Combined heart-lung transplantation for end-stage Eisenmenger's syndrome. J Thorac Cardiovasc Surg 1986;91:443–50.
7. Yacoub MH, Khaghani A, Miyamura H, Sono J. Heart-lung transplantation; Harefield experience. Jpn J Surg 1990;20:247–51.
8. Fremes SE, Patterson GA, Williams WG, et al. Single lung transplantation and closure of patent ductus arteriosus for Eisenmenger's syndrome. J Thorac Cardiovasc Surg 1990;100: 1–5.
9. Pollack KL, Chestnut DH, Wenstrom KD. Anesthetic management of a parturient with Eisenmenger's syndrome. Anesth Analg 1990;70:212–5.
10. Lieber S, Dewilde P, Huyghens L, Tracy E, Gepts E. Eisenmenger's syndrome and pregnancy. Acta Cardiol (Brux) 1985; 40:421–4.
11. Midwall J, Jaffin H, Herman MV, Kupersmith J. Shunt flow and pulmonary hemodynamics during labor and delivery in the Eisenmenger syndrome. Am J Cardiol 1978;42:299–303.
12. Jones AM, Howitt G. Eisenmenger syndrome in pregnancy. Br Med J (Clin Res) 1965;1:1627–31.
13. Neilson G, Galea EG, Blunt A. Eisenmenger's syndrome and pregnancy. Med J Aust 1971;1:431–4.
14. Pitts JA, Crosby WM, Basta LL. Eisenmenger's syndrome in pregnancy. Am Heart J 1977;93:321–6.
15. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34:721–41.
16. Spinnato JA, Kraynack BJ, Cooper MW. Eisenmenger's syndrome in pregnancy: epidural anesthesia for elective cesarean section. N Engl J Med 1981;304:1215–7.
17. Devitt JH, Noble WH, Byrick RJ. A Swan-Ganz catheter related complication in a patient with Eisenmenger's syndrome. Anesthesiology 1982;57:335–7.
18. Weber RK, Buda AJ, Levene DL. General anesthesia in Eisenmenger's syndrome. Can Med Assoc J 1977;117:1413–4.
19. Bird TM, Strunin L. Anaesthesia for a patient with Down's syndrome and Eisenmenger's complex. Anaesthesia 1984;39: 48–50.
20. Skinner DH, Tremper KK, Cullen BF. Transcutaneous pO_2 monitoring in the anesthetic management of a patient with Eisenmenger's syndrome. Crit Care Med 1985;13:608–9.
21. Lumley J, Whitwam JG, Morgan M. General anesthesia in the presence of Eisenmenger's syndrome. Anesth Analg 1977;56: 543–7.
22. Kraayenbrink MA, Steven CM. Anaesthesia for carotid body tumour resection in a patient with the Eisenmenger syndrome. Anaesthesia 1985;40:1194–7.
23. Selsby DS, Sugden JC. Epidural anaesthesia for bilateral inguinal herniorrhaphy in Eisenmenger's syndrome. Anaesthesia 1989;44:130–2.
24. Foster JM, Jones RM. The anaesthetic management of the Eisenmenger syndrome. Ann R Coll Surg Engl 1984;66:353–5.
25. Eisenmenger V. Congenital defects of the ventricular septum. Z Clin Med Suppl 1897;32:1–28.
26. Hallidie-Smith KA, Goodwin JF. The Eisenmenger syndrome. Prog Cardiol 1974;3:211–25.
27. Wong CK, Lau CP, Leung WH, Cheng CH. The use of nifedipine in patients with Eisenmenger's syndrome complicating patency of the arterial duct. Int J Cardiol 1989;25:173–8.
28. Blake S, Bonar SF, Blake P, Garrett J. The effect of a peripheral vasoconstrictor drug on the systemic arterial oxygen saturation in Eisenmenger's syndrome. Ir J Med Sci 1984;153:319–20.
29. Sethi KK, Kulshreshtha A, Gupta MP. Recurrent paradoxic embolism in Eisenmenger syndrome. Indian Heart J 1984;36: 121–3.
30. Cucchiara RF, Nugent M, Seward JB, Messick JM. Air embolism in upright neurosurgical patients: detection and localization by two-dimensional transesophageal echocardiography. Anesthesiology 1984;60:353–5.
31. Dajani AS, Bisno AL, Chung KJ, et al. Prevention of bacterial endocarditis; recommendations by the American Heart Association. JAMA 1990;264:2919–22.
32. Robinson S. Pulmonary artery catheters in Eisenmenger's syndrome: many risks, few benefits (correspondence). Anesthesiology 1983;58:588–9.
33. Barash PG, Nardi D, Hammond G, et al. Catheter-induced pulmonary perforation; mechanisms, management, and modifications. J Thorac Cardiovasc Surg 1981;82:5–12.
34. Shah KB, Rao TLK, Laughlin S, El-Etr AA. A review of pulmonary artery catheterization in 6,245 patients. Anesthesiology 1984;61:271–5.
35. Chastre J, Cornud F, Bouchama A, Viau F, Benacerraf R, Gebert C. Thrombosis as a complication of pulmonary artery catheterization via the internal jugular vein. N Engl J Med 1982;306:278–81.

Letters to the Editor

A "New" Needle?

To the Editor:

In your January 1992 issue, a letter by Eldor, Guedj, and Gozal (1) described what appeared to be a new concept: to perform a subarachnoid block in parturient patients, followed by the insertion of a catheter into the epidural space for later injection of local anesthetics. This was accomplished with one single puncture done through a special needle. It happens that neither the concept nor the needle are new; Torrieri and Aldrete (2) first reported them, and Eldor and Chaimsky (3) wrote a similar paper that was published a few months later.

Eldor, Gozal, Guedj, Pode, and Cotev (4) wrote almost the same description of the "new" concept and the "new" needle used in 13 patients having prostatectomy without mentioning the earlier descriptions, nor cross-referencing their own, earlier or late publication.

Perhaps even for letters to the editor, authors should be required to sign a statement indicating that their "novelties" are not being published simultaneously elsewhere.

Let editors follow their own precepts as noted on their own editorial (5).

J. Antonio Aldrete, MD, MS
Pain Management Center
Humana Hospital-Destin
Destin, FL 32541

A. Torrieri, MD
Anchorena 1586-8° A
(1425) Capital Federal
Republic of Argentina

References

1. Eldor J, Guedj P, Gozal Y. Combined spinal-epidural anesthesia using the CSEN. Anesth Analg 1992;74:169–70.
2. Torrieri A, Aldrete JA. The T-A pair needle. Acta Anaesthesiol Belg 1988;39:65–6.
3. Eldor J, Chaimsky G. Combined spinal-epidural needle (CSEN). Can Anaesth Soc J 1988;35:537–8.
4. Eldor J, Gozal Y, Guedj P, Pode D, Cotev S. Combined spinal-epidural anesthesia with a specialized needle. Reg Anesth 1991;16:348–9.
5. Smith G, Miller R, Saidman L, Morgan M. Ethics in publishing. Anesthesiology 1991;74:637–8.

In Response:

Thank you for the opportunity to respond to the letter of Drs. Aldrete and Torrieri concerning our experience with the new combined spinal epidural needle (CSEN) (1).

First, I would like to start from the end: Drs. Torrieri and Aldrete published a similar letter 3 years ago (2); so, this letter can be regarded as a duplication, although they didn't mention their previous letter in their references. They have written that "it appears that the concept has been grasped all over the world." I fully agree. However, it seems that they are lacking some information concerning the combined spinal-epidural needle.

Before January 1988 I sent a description of the "old" CSEN to the American Society of Regional Anesthesia which was published as an abstract (3), so that Drs. Aldrete and Torrieri cannot claim to have published before me on the basis of their letter (4). Besides, on their original publication there is no title. They added a title to their letter written 4 years later. Is this permissible according to "ethics in publishing" (5)?

However, the picture is more complicated. In July 1987, Dennis W. Coombs and Neurodelivery Technology Inc., Tempe, Arizona, applied for a patent of a multilumen epidural-spinal needle (6). A letter concerning this needle was published in this journal (7). It is correct that all three needles described above (the CSEN, Torrieri and Aldrete's, and Coombs') are similar. However, they are different from the new CSEN, the "Eldor needle," and that is the reason for this letter.

I am sorry that Drs. Aldrete and Torrieri didn't understand the difference between the "old" CSEN, which we described 4 years ago (8), and the new CSEN, named the Eldor needle. I have abandoned the concept of the old CSEN because of the danger of metallic particles in the spinal-epidural spaces using the needle-through-needle approach (9). In the old CSEN, as well as in the needles of Torrieri and Aldrete and of Coombs, some parts of the spinal conduit are bent. This can produce metallic particles because friction is created when the spinal needle is introduced through it.

In the Eldor needle, which is the new CSEN, the guide spinal tube is straight and is positioned at the side of the needle. This shortens the distance between the tips of the epidural and the spinal needles, thus preventing bone puncture.

Anyone who compares the drawings of the old CSEN (8) to that of the new CSEN (Eldor needle) (1) will notice the principal differences. That is why there was no need to mention the old CSEN in the clinical description of the use of the new CSEN. And that is why I didn't mention the needle of Drs. Torrieri and Aldrete.

Finally, some words about novelties and inventiveness: the letter describing the use of the Eldor needle in 10 parturients for cesarean section (1) and that describing its use in 13 patients scheduled for prostatectomy (10) are the first descriptions ever of its clinical use. There was only one early description (in French) (11) and this was of the needle per se and not of its clinical use.

I don't think that examining the Eldor needle in young patients and old patients is a duplication of results that needs signing, as Drs. Aldrete and Torrieri suggest. According to their logic, every paper testing the Tuohy needle is also a duplication.

I agree with Drs. Aldrete and Torrieri that letters to the

©1992 by the International Anesthesia Research Society

editor should include a statement that they are not being published simultaneously elsewhere, because I think sometimes letters are more important and more vivid . . . as I hope is the case with this one.

Joseph Eldor, MD
Department of Anesthesia
Misgav Ladach General Hospital
P.O. Box 12142
Jerusalem 91120
Israel

References

1. Eldor J, Guedj P, Gozal Y. Combined spinal-epidural anesthesia using the CSEN. Anesth Analg 1992;74:169–70.
2. Torrieri A, Aldrete JA. Combined spinal-epidural needle. Can J Anaesth 1989;36:483.
3. Eldor J. Combined spinal-epidural needle. Reg Anesth J 1988;15:89.
4. Torrieri A, Aldrete JA. The T-A pair needle. Acta Anaesthesiol Belg 1988;39:65–6.
5. Smith G, Miller R, Saidman L, Morgan M. Ethics in publishing. Anesthesiology 1991;74:637–8.
6. Coombs DW. Method for making a multi-lumen epidural-spinal needle and tip and stock configuration for the same. 1990: U.S. patent No. 4,958,901.
7. Bleck G. New needle for combined epidural and spinal techniques. Anesth Analg 1990;70:128.
8. Eldor J, Chaimsky G. Combined spinal-epidural needle (CSEN). Can Anaesth Soc J 1988;35:537–8.
9. Eldor J, Brodsky V. Danger of metallic particles in the spinal-epidural spaces using the needle-through-needle approach. Acta Anaesthesiol Scand 1991;35:461.
10. Eldor J, Gozal Y, Guedj P, Pode D, Cotev S. Combined spinal-epidural anesthesia with a specialized needle. Reg Anesth 1991;16:348–9.
11. Eldor J, Guedj P. Une nouvelle aiguille pour l'anesthesie rachidienne et peridurale conjointe. Ann Fr Anesth Reanim 1990;9:571–2.

A Simple Method of MDI Administration in the Intubated Patient

To the Editor:

Metered dose inhalers (MDI) are currently appropriate alternatives to nebulizers for the administration of aerosolized bronchodilators because of their lower cost and relative ease of use. Several adapters are available to allow MDI use via the anesthesia circuit or endotracheal tube (ETT) of a tracheally intubated patient. A significant problem with the MDIs involves the low percentage and variability of actual drug delivery to the lungs. Much of the drug is deposited in the oropharynx of the nonintubated patient. In an intubated patient, the majority is deposited in the ETT or elbow connector. Estimates of drug delivery to the lung via MDI circuit adapters have ranged from 2.5% to 12.3% (1–3) of the discharged dose, with variables including diameter and length of ETT, phase of ventilation, type of actuator, and drug particle size.

A previously described method (3,4) of MDI administration via a catheter ensures more efficient drug delivery for intubated patients. We would like to introduce a simple clinical system that allows utilization of this catheter method. Components include the standard MDI canister with a 35- or 60-mL syringe, a 12-in. 18-gauge intravenous catheter (different lengths may be required), and a bronchoscopy elbow port adapter (Figure 1). The intravenous

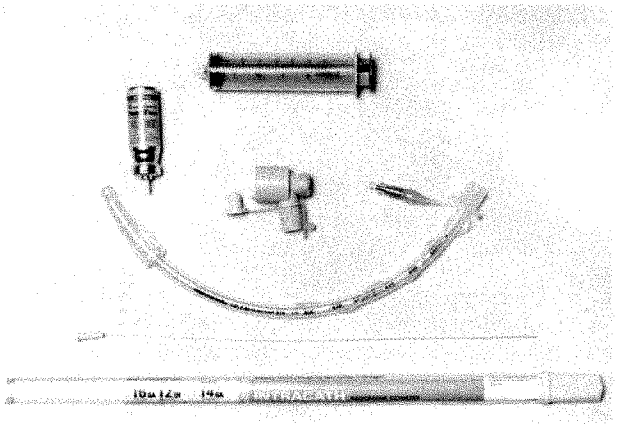


Figure 1. Individual components of the MDI administration system.

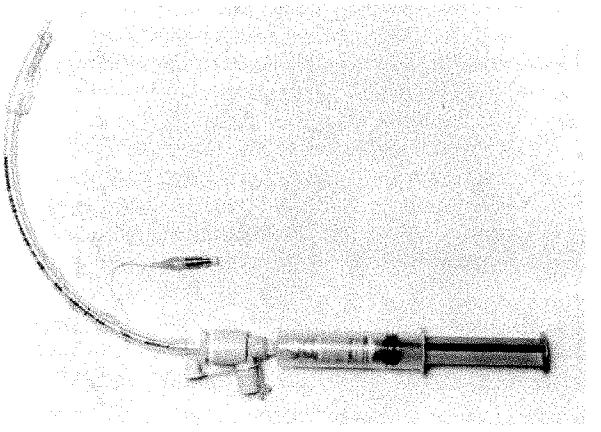


Figure 2. Combined units of the MDI delivery system. Note the tip of the catheter extending a short distance beyond the tip of the endotracheal tube.

catheter is connected to the syringe. The canister fits easily into the barrel of the syringe with the plunger acting as a trigger. The catheter is passed through the port adapter and down the ETT, where the MDI can be discharged by simply pushing on the plunger (Figure 2). Just as in routine oral use, bronchodilator discharge is maximally effective when the canister is in the upright position. Catheter length and placement should allow optimal drug delivery: outside the distal tip of the ETT and above the carina. Therefore, catheter length may vary according to anatomic variation and ETT length. The bronchoscopy adapter allows repeated administrations of drug during the inspiratory phase without excessive manipulation of the circuit. The circuit sampling port for the mass spectrometry or end-tidal CO_2 may allow passage of the catheter to the ETT tip as well. By minimizing drug exposure to the circuit and ETT, drug delivery should be considerably more efficient. Indeed, laboratory evaluations using the MDI with various extensions and catheters have shown improved estimated drug delivery to the lung ranging from 23.3% (4) to 96.7% (3). Based on this increased delivery efficiency, we recommend administration of no more than 2 puffs at a 30-min

dosing interval in adult patients to minimize the risk of toxicity using this method of delivery.

Edwin Dunteman, MD, MS
George Despotis, MD
Department of Anesthesiology
Washington University School of Medicine
660 South Euclid
Box 8054
St. Louis, MO 63110

References

1. Bishop MJ, Larson RP, Bushman DL. Metered dose inhaler aerosol characteristics are affected by endotracheal tube actuator adapter used. Anesthesiology 1990;73:1263–5.
2. Crogan SJ, Bishop MJ. Delivery efficiency of metered dose aerosols given via endotracheal tubes. Anesthesiology 1989;70:1008–10.
3. Taylor RH, Lerman J. High-efficiency delivery of salbutamol with a metered-dose inhaler in narrow tracheal tubes and catheters. Anesthesiology 1991;74:360–3.
4. Peterfreund RA. A simple catheter extension improves delivery efficiency of metered dose inhalers: a quantitative evaluation (abstract). Anesthesiology 1990;73:A486.

Reliability of the Slope of the End-Systolic Pressure-Volume Relationship as Individual Index of Myocardial Inotropic State

To the Editor:

Mulier et al. (1) compared the cardiodynamic effects of propofol and thiopental in humans with a transesophageal echocardiographic approach. They used the end-systolic pressure-volume relationship (ESPVR) for measurement of myocardial contractility. The variables defining the ESPVR are its slope (Emax) and its intercept with the volume axis (V_0). Apparently, the authors only once calculated the volume axis intercept, i.e., at baseline, and assumed this intercept to remain constant throughout their protocol.

Controversy exists as to which of the two variables, Emax or V_0, is the more reliable indicator of inotropic state. Altered inotropic state has been shown to affect Emax with no significant changes in V_0 in isolated canine left ventricles (2) and in open-chest dogs (3). Similar results have also been reported in conscious dogs (4) and in humans (5). Other studies, however, are less straightforward. Grossman et al. (6) reported significant changes in both Emax and V_0 with changing contractile state. Kass et al. (7) obtained similar results. Sagawa et al. (8) observed that both changes in Emax and a parallel shift of the ESPVR occurred with changes in contractility. This inconsistency of the slope and the volume intercept of the ESPVR as individual indexes of inotropic state has been confirmed by Crottogini et al. (9), who proposed the area beneath the ESPVR as a most consistent indicator of variations in inotropic state. It is of interest to note that the linearity of the ESPVR is now also questioned as improved techniques for ESPVR measurement have increasingly revealed a nonlinear relationship (10,11).

The complexity of the ESPVR is such that one should not rely on Emax as the single variable to demonstrate changes in myocardial contractility. Therefore, we believe that the authors should have ascertained that no concomitant shift of V_0 had occurred with administration of propofol and thiopental. Calculation of V_0 at each stage of the protocol, instead of assuming a constant V_0, would have added to the value of their results and provided a more irrefutable confirmation of the negative inotropic effects of propofol.

Stefan G. De Hert, MD, PhD
Karel M. Vermeyen, MD, PhD
Department of Anesthesiology
University Hospital Antwerp
Wilrijkstraat 10
B-2650 Edegem
Belgium

References

1. Mulier JP, Wouters PF, Van Aken H, Vermaut G, Vandermeersch E. Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. Anesth Analg 1991;72:28–35.
2. Suga H, Sagawa K, Shoukas A. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973;32:314–22.
3. Kaseda S, Tomoike H, Ogata I, Nakamura M. End-systolic pressure-volume, pressure-length and strain-stress relations in canine hearts. Am J Physiol 1985;249:H648–54.
4. Sodums MT, Badke FR, Starling MR, Little WC, O'Rourke RA. Evaluation of left ventricular contractile performance utilizing end-systolic pressure-volume relations. Circ Res 1984;54:731–9.
5. Mehmel HC, Stocknis B, Ruffmann K, von Olshausen K, Schuler G, Kubler W. The linearity of the end-systolic pressure-volume relationship in man and its sensitivity for assessment of left ventricular function. Circulation 1981;63:1216–22.
6. Grossman W, Braunwald E, Mann T, McLaurin LP, Green LW. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. Circulation 1977;56:845–52.
7. Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. Circulation 1986;73:586–95.
8. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure-volume ratio: a new index for contractility. Am J Cardiol 1979;40:748–53.
9. Crottogini AJ, Willshaw P, Barra JG, Armentano R, Cabrera Fisher EI, Pichel RH. Inconsistency of the slope and the volume intercept of the end-systolic pressure-volume relationship as individual indexes of inotropic state in conscious dogs: presentation of an index combining both variables. Circulation 1987;76:1115–26.
10. Burkhoff D, Sugiura S, Yue DT, Sagawa K. Contractility-dependent curvilinearity of end-systolic pressure-volume relations. Am J Physiol 1987;252:H1218–27.
11. Kass DA, Beyar R, Lankford E, Heard M, Maughan WL, Sagawa K. Influence of contractile state on curvilinearity of in situ end-systolic pressure-volume relations. Circulation 1989;79:167–78.

A response was solicited from Dr. Mulier, but he has not responded.

Use of a Wilson Convex Frame in Removing "Irretrievable" Epidural Catheters

To the Editor:

The anesthesia literature contains numerous case reports of difficulties removing epidural and spinal catheters. A recent letter to the editor described a method for removing otherwise irretrievable epidural catheters by passing a Tuohy needle over the catheter (1). As Shantha et al. suggest, shearing of the catheter resulting in the retention of catheter parts within the neuroaxis is a distinct possibil-

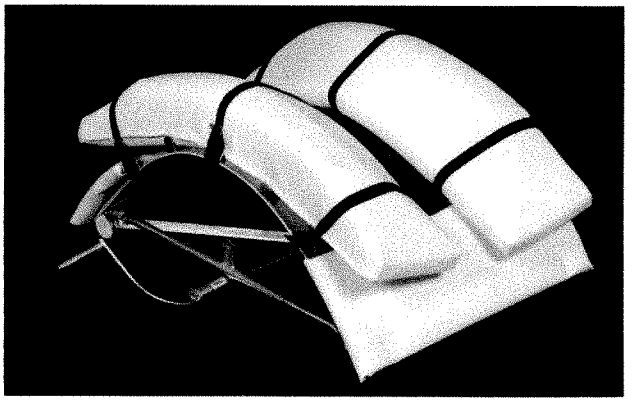


Figure 1. Wilson Convex Frame.

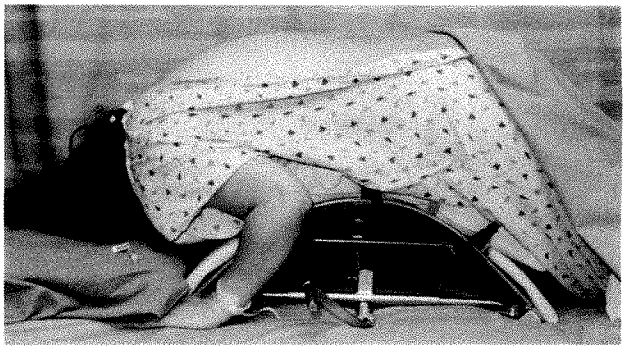


Figure 2. Wilson Convex Frame in use.

ity. Before such an invasive and possibly disastrous method of catheter extraction is undertaken, we believe that other noninvasive means should first be attempted. We report the successful use of a noninvasive method for catheter retrieval using a Wilson Convex Frame (Zimmer, Statesville, N.C.).

Case 1. A 21-yr-old woman with a term pregnancy requested epidural anesthesia for relief of labor pain. She had a history of scoliosis that was not evident on physical examination. Placement of a 20-gauge multiorifice epidural catheter through an 18-gauge Tuohy-Schliff needle via a midline approach at the L2-3 interspace was successful on the third attempt. The first two attempts were abandoned after the aspiration of blood from the in situ catheters. The catheter was advanced 4 cm cephalad into the epidural space without difficulty. Good segmental anesthesia to the T-10 level was obtained with bupivacaine. After vaginal delivery, initial attempts to remove the catheter were not successful. Several anesthesiologists tried to remove the catheter after placing the patient in a variety of positions (left and right lateral decubitus position with flexion, sitting, kneeling with hands down and back flexed, and variations with her back extended). Attempts at catheter removal were discontinued after it was apparent that traction on the catheter was resulting in catheter lengthening. We reasoned that back muscle and ligament tension could cause a narrowing of the intervertebral spaces, thereby crimping the catheter. We further postulated that if the patient's back could be flexed while her muscles and ligaments were relaxed, then the catheter could be extracted. A Wilson Convex Frame (Figure 1) was obtained and placed on a gurney. The frame was adjusted to allow for maximal flexion. The patient was positioned prone over the frame (Figure 2) and allowed to relax for a few minutes. The catheter was then removed intact on the first attempt with minimal resistance and no further catheter lengthening. No defect in the catheter was present. Further anesthesia care was not required.

Case 2. A 22-yr-old woman with a term pregnancy opted for epidural anesthesia for labor pain management. A 20-gauge epidural catheter was easily threaded cephalad 4 cm through an 18-gauge Tuohy-Schliff needle via a midline approach at the L3-4 interspace. Excellent analgesia was obtained with a continuous infusion of bupivacaine/sufentanil. Vaginal delivery was uncomplicated. As in the first case, the catheter was resistant to removal. Catheter stretching was evident during the attempted removal. Once again, multiple patient positions were tried, but to no avail. Based on the experience of the prior case, the Wilson Convex Frame was used in the manner described above. The intact catheter was then extracted from the patient without difficulty.

The Wilson Convex Frame is a positioning device frequently utilized for back surgery. It allows the patient's back to be in a flexed position while paraspinal muscles and ligaments are relaxed. Application of the frame allowed us to easily withdraw two apparently irretrievable epidural catheters. We recommend this simple, noninvasive technique before resorting to more invasive methods that could result in catheter shearing.

Robert J. Start, MD
Daniel J. Greenberg, MD
Norman L. Herman, MD, PhD
Department of Anesthesiology/SGHSA
Wilford Hall USAF Medical Center
Lackland AFB, TX 78236-5300

Reference

1. Shantha TR, Mani M. A simple method to retrieve irretrievable epidural catheters. Anesth Analg 1991;73:508–9.

Labeling of Syringes to Prevent "Drug Swaps"

To the Editor:

Accidental injection of the wrong drug ("drug swap") is one of the most common errors committed by anesthesiologists. To reduce the likelihood for this error, I began instructing residents to label syringes with the drug label partially overlying the graduated volume markings (as shown on the bottom syringe in Figure 1). Placing the drug label in this position allows the drug name to be read (and even prompts the drug name to be read) as the drug is being injected. This is in contrast to the situation where the drug label is placed on the back side of the syringe away from the graduated markings (as in the top syringe). I find that residents usually place the label in this position so as

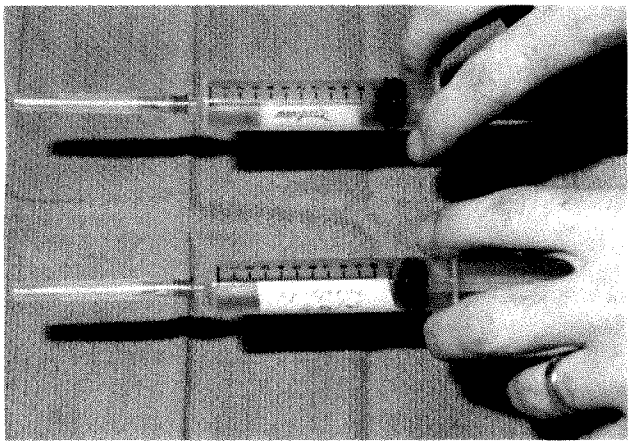


Figure 1. Labeled syringes.

not to "obscure" the graduated markings. With this arrangement, the face of the drug label is not visible during syringe injections unless the syringe is rotated 180° during the injection process. Labeling the syringes with the label partially overlying the graduated markings also provides easy visibility of the drug labels when the syringes are placed on a flat surface. This is obviously a simple suggestion, yet it could prevent some serious mistakes.

Terry W. Latson, MD
Department of Anesthesiology
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, TX 75235-8894

A Simple Device to Demonstrate the Law of Laplace

To the Editor:

The law of Laplace can be summarized in the following equation: $P = 2T/R$, where P is the pressure within a bubble, T is its surface tension, and R is the radius of the bubble (1). This law applies to the functioning of many organs and structures in the body, including the cardiac chambers and the pulmonary alveoli. Although Laplace's law is ubiquitous and commonly referenced in anesthesia, many find it difficult to conceptualize. To facilitate its understanding, we have designed a simple device to aid in illustrating the implications of this law (see Figure 1).

One can take the barrel of a syringe and cut off both ends with a saw. An orifice is drilled in the middle of the barrel. Two similar balloons are slipped over each end and secured with tape. They are inflated by blowing through the orifice which is then quickly covered by a finger. By squeezing one balloon against the other, one can tangibly experience the radius, wall tension, wall thickness, distending pressure, and compliance of each balloon. Furthermore, one can appreciate that the smaller balloon tends to empty into the larger balloon and that more pressure is required to expand the smaller one. This device has been particularly useful in teaching pulmonary alveolar physiology and cardiac ventricular function in the anesthesia classroom.



Figure 1. The thumb is obstructing the orifice to prevent the balloons from deflating.

Rafael Ortega, MD
Department of Anesthesiology
Boston University Medical Center
88 East Newton Street
Boston, MA 02118

Reference

1. Nunn JF. Applied respiratory physiology. 3rd ed. London: Butterworths, 1987:23–45.

The 3.5/4.5 Modification for Fiberscope-Guided Tracheal Intubation Using the Laryngeal Mask Airway

To the Editor:

We read with interest the letter by Benumof (1), concerning using the laryngeal mask airway (LMA) to facilitate fiberoptic tracheal intubation. We have used a modified technique that allows removal of the LMA while retaining the endotracheal tube (ETT) for intraoral surgery.

Ordinarily, there is insufficient length of exposed ETT to allow the anesthesiologist to grasp the tube in the mouth before the proximal end is lost within the LMA. To overcome this problem in our pediatric practice, we have devised the "3.5/4.5" solution. This combination of tracheal tube sizes acts as "extenders" for a previously placed tracheal tube. After fiberoptic intubation through the LMA, the bronchoscope is withdrawn and an extender is pressed

into or over the exposed proximal end of the tracheal tube. The LMA is then removed over the extended tracheal tube. The extender is replaced by a standard connector and the patient is reattached to the anesthetic circuit.

Using an Olympus PF-27 S bronchoscope through a size 2 LMA, intubation can be achieved with tube sizes of 3.5–4.5-mm ID. The 3.5-mm-ID ETT can be extended with a 4.5-mm-ID ETT placed over the outside of the positioned ETT. Similarly, a 4.5-mm-ID ETT can be extended with a 3.5-mm ETT inside the existing ETT. A cuffed 6.0-mm ETT will pass through the size 3 and size 4 LMA, and a 5.0-mm tube placed inside acts as a suitable extender. Should the size of the ETT be inadequate, either a gum elastic bougie or a tracheal tube exchanger can be inserted within the ETT and exchanged for the appropriate-sized tube.

It is a prerequisite to success in this technique that the LMA is correctly positioned in the patient (2). We encourage anesthesiologists to develop skills in inserting, positioning, and maintaining the airway via the LMA in routine cases before attempting this technique on a potentially difficult airway.

Graham D. Chadd, MB, ChB
Andrew J. Walford, MB, ChB
David L. Crane, MD
Department of Anesthesiology
The Children's Hospital of Oklahoma
940 NE 13th Street, 4 Bielstein, Room 138
Oklahoma City, OK 73104

References

1. Benumof JL. Use of the laryngeal mask airway to facilitate fiberscope aided tracheal intubation. Anesth Analg 1992;74:313–4.
2. Brain AIJ. Studies on the laryngeal mask; first, learn the art. Anaesthesia 1991;46:417–8.

Effect of Propofol in Brainstem Auditory Evoked Responses

To the Editor:

Dr. Thornton and his colleagues studied the effect of propofol (Diprivan) to assess its effect on brainstem auditory evoked responses (BAERS) (1). They noted prolongation of wave III and V latencies with normal III–V interpeak interval. They concluded that propofol has little effect on the brainstem in that the III–V interpeak interval did not change significantly. However, no explanation was given for the delayed latencies of waves III and V. Further, it is not clear from the report whether the I–III interpeak latency, which is a measure of lower brainstem transmission, was prolonged or not. Savoia et al. (2) noted that wave I latency was increased and they attributed this to the effect of nitrous oxide. Chassard et al. (3) noted that peak latencies of I, III, and V increased significantly compared with control values but interpeak intervals were not significantly affected. They concluded that this was an indication of delayed neuronal events, probably at the sites of synaptic transmission, and a definite alteration in brainstem function. The patients in these studies were all premedicated and the patients in the studies by Thornton et al. and Savoia et al. received other anesthetic agents in addition to propofol.

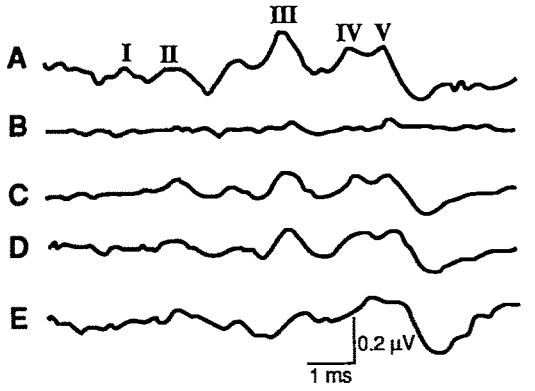


Figure 1. Brainstem auditory evoked responses. **A.** Preoperative (normal). **B.** Intraoperative, showing marked wave suppression. **C, D.** Return of waveforms and prolongation of wave I. **E.** Two hours after surgery demonstrating return of all waves. Latency of wave I remains prolonged.

We monitored BAERS in five patients who were unpremedicated and received single intravenous bolus doses of propofol (2 mg/kg) just before preauricular facial and retrobulbar blocks for cataract surgery. In the first minute after the administration of propofol, all the waves were suppressed in one patient (Figure 1); all the waves except wave V were suppressed in another patient; and wave II was abolished in all five patients. In four patients the latency of wave I was prolonged for several hours. All the patients were apneic in the first minute after the intravenous bolus. The interpeak intervals were not prolonged. Our findings suggest that propofol suppresses at least the lower brainstem, abolition of wave II indicating medullary suppression. This probably supports the clinical observation of apnea in a significant number of these patients. The prolongation of wave I suggests the possibility of an endocochlear effect of propofol (4). We believe that in the study of Savoia et al. (2) the prolongation of wave I was at least partly due to the effect of propofol. In the study reported by Chassard et al. (3), because interpeak latencies were not significantly prolonged, the prolongation of the latencies of waves I, III, and V was due simply to prolongation of wave I.

These observations at least suggest caution in the use of propofol for brainstem surgical procedures. Prospective studies, both long and short term, of unpremedicated patients who receive only the propofol are warranted.

R. V. Reddy, MD
S. S. Moorthy, MD
S. F. Dierdorf, MD
R. D. Yee, MD
Linda Link, EEG-EPT
Departments of Neurology, Anesthesiology, and Ophthalmology
RLR, VA Medical Center and Indiana University Medical Center
1481 West 10th Street
Indianapolis, IN 46202

References

1. Thornton C, Konieczko KM, Knight AB, et al. The effect of Diprivan on the auditory evoked response. European Congress of Anaesthesiology, Vienna, September 7–13, 1986: abstract 11.

2. Savoia G, Esposito C, Belfiore F, et al. Propofol infusion and auditory evoked potentials. Anaesthesia 1983;43(Suppl):46–9.
3. Chassard D, Joubaud A, Colson A, et al. Auditory evoked potentials during propofol anesthesia in man. Br J Anaesth 1989;69:522–6.
4. Guerit JM, Mahieu P, Houben-Giurgea S, et al. The influence of ototoxic drugs on brainstem auditory evoked potentials in man. Arch Otorhinolaryngol 1981;233:189–99.

When Is a Fact, in Fact, a Fact?

To the Editor:

An editorial in a peer-reviewed journal such as *Anesthesia & Analgesia* has the ring of truth, handed down. Thus when I came across the "fact" that hypokalemic patients had an increased incidence of ventricular arrhythmias with hypoxemia (Sao_2 saturation < 90%) (1), I wanted to believe that this fact, like many others, had simply escaped me.

Curiosity got the better of me, however. I was amazed to find in the referenced article (2), absolutely nothing supporting the above "fact." Indeed, the article, which discusses ventricular ectopy in sleep apnea patients, contains the following: "While diuretics were being used to treat hypertension in 15 patients (48%), all patients were normokalemic." The summary includes this finding: "The PVC frequency showed no statistically significant increase until the Po_2 fell below 60%."

Now, hypokalemic patients may *have* an increased frequency of ventricular arrhythmias in the presence of hypoxemia, but the referenced article is not the evidence promised.

J. Bruce Laubach, MD
Department of Anesthesiology
Baylor University Medical Center
3600 Gaston Avenue
Dallas, TX 75246

References

1. Scuderi PE, Bowton DL, Anderson RL, Prough DS. Pulse oximetry: would further technical alterations improve patient outcomes? Anesth Analg 1992;74:177–80.
2. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest 1985;88:335–40.

In Response:

In reply to the letter by Dr. Laubach regarding our editorial, there was, indeed, an error in reference citation. The sentence in which our references to Dr. Shepard's papers (References 14 and 15) appear was, unfortunately, transposed during our final editing. We apologize for the error. The reference for an increase in ventricular ectopy with hypokalemia should be Reference 15 (Shepard JW Jr, et al., American Journal of Medicine [1]), in which Dr. Shepard and colleagues demonstrate a reproducible increase in ventricular ectopy in a hypokalemic patient with chronic obstructive pulmonary disease with desaturation to < 90%. Similarly, the absence of ventricular ectopy with desaturation to < 80% (Shepard JW Jr, et al., Chest 1985 [2]) refers to patients with obstructive sleep apnea.

We regret that this error was not caught in proofreading. We thank Dr. Laubach for bringing this to our attention.

Phillip E. Scuderi, MD
Donald S. Prough, MD
David L. Bowton, MD
Randy L. Anderson, PhD
Department of Anesthesia
Bowman Gray School of Medicine
Wake Forest University
Medical Center Boulevard
Winston-Salem, NC 27157-1009

References

1. Shepard JW Jr, Garrison MW, Grither DA, Evans R, Schweitzer PK. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. Am J Med 1985;78:28–34.
2. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest 1985;88:335–40.

Plug It In!

To the Editor:

Eckhardt et al. (1) are to be commended for bringing to our attention the migration of an esophageal stethoscope as a possible cause of small bowel obstruction. They suggest taping monitoring devices or using retention devices to prevent such occurrences. I respectfully suggest another technique—keeping the esophageal stethoscope in continuity with the anesthesia care provider's ear!

I have observed that over the past 10 years this has become a less common practice. Reliance is placed upon more sophisticated (i.e., electronic) monitors and less attention to direct patient monitoring using one's own senses. Although we cannot so accurately quantify respiratory and cardiovascular parameters using an esophageal stethoscope, it does offer an unpowered, continuous, and reliable means of assessing cardiopulmonary status (at least to the extent of go/no-go). It must, however, be continuously "plugged in" to the anesthetist who must be "turned on" to accrue this information. It provides invaluable feedback during periods of anesthetic practice when monitoring may be relatively austere, as in patient transport, practice in developing countries, and during military deployments.

Plug it in! A simple remedy for esophageal stethoscope migration and enhanced patient care.

Shepard B. Stone, MPS, PA
Department of Anesthesiology
Yale-New Haven Hospital
Yale University School of Medicine
333 Cedar Street
P.O. Box 3333
New Haven, CT 06510

Reference

1. Ekhardt WF, Patafio O, Cigarroa FG. A retained esophaeal stethoscope as a potential cause of small bowel obstruction. Anesth Analg 1992;74:300–2.

In Response:

We appreciate Mr. Shepard Stone's remarks regarding patient monitoring with an esophageal stethoscope. We agree that continuous monitoring with a stethoscope is the goal, and this would have possibly prevented our complication. However, in complex cases such as cardiac surgery, liver transplantation, and trauma resuscitation, the myriad of other tasks and duties that must be performed make continuous monitoring with an esophageal stethoscope impossible. In these cases, it seems reasonable to anchor the stethoscope with tape, and intermittently monitor the patient with it.

William F. Eckhardt, MD
Onofrio Patafio, MD
Francisco Cigarroa, MD
Department of Anesthesia
Massachusetts General Hospital
Fruit Street
Boston, MA 02114

What Caused the Unilateral Epidurogram and Bilateral Epidural Analgesia?

To the Editor:

We have read with interest the case report written by Peduto et al. (1). They described a case of bilateral analgesia and unilateral motor and sympathetic blockade after continuous lumbar epidural anesthesia with the radiologic confirmation of unilateral spread of the contrast medium. To explain their observations that the postoperative contrast image was not compatible with the development of clinical features, they hypothesized and concluded as follows: (a) Unilateral contrast image resulted from the presence of a dorsal midline band which acted as a diffusion barrier to the contrast medium. (b) Local anesthetics injected into the epidural space should extend only on the right side. (c) Left-sided analgesia might have resulted from the development of blockade for the pain sensation that originated from the left side within the spinal cord.

We have a different idea as to the cause of the unusual clinical features. Their hypothesis can be challenged on the basis of the method of drug injection; contrast medium was injected through the epidural catheter, whereas the local anesthetic was injected through both the epidural needle and the catheter. In our opinion, first of all, the bolus injection of local anesthetics (12 mL of 0.5% bupivacaine) through the needle did cause the bilateral spread of anesthetic solution and the subsequent bilateral analgesia. Second, when an epidural catheter is inserted 2 cm into the epidural space, the tip of the catheter would be located in the anterior epidural space. Thus, injection of an additional local anesthetic (5 mL of 0.5% bupivacaine) would extend in the cephalocaudad direction along the spinal canal rather than in the circumferential direction around the dura, and subsequent profound unilateral motor and sympathetic blockade would develop. This observation has been reported in animal experiments (2). If the location of the catheter tip or a lateral view of the contrast image had been examined by Peduto et al., the etiology of the clinical features could have been clarified. Recently, we also confirmed radiographically the location of a catheter tip in the anterior epidural space in a patient who showed unilateral epidural blockade from the T-10 to L-5 and S-2 to S-4 dermatomes (unpublished data). In addition, we reported that the median epidural septum is not a common cause of unilateral epidural blockade (3). We believe that the development of the unilateral contrast image was caused by the longitudinal spread of the contrast medium because of the location of the catheter tip in the anterior epidural space, not by the dorsal midline band.

Fumio Asato, MD, PhD
Fumio Goto, MD, PhD
Department of Anesthesiology
School of Medicine
Kitasato University
1-15-1 Kitasato, Sagamihara, Kanagawa, 228
Japan

References

1. Peduto VA, Tani R, Marinelli L, Pani S. Bilateral analgesia and unilateral paresis after lumbar epidural blockade. Anesth Analg 1992;74:294–6.
2. Usubiaga JE, Dos Reis A, Usubiaga LE. Epidural misplacement of catheters and mechanisms of unilateral block. Anesthesiology 1970;32: 158–61.
3. Asato F, Hirakawa N, Oda M, et al. A median epidural septum is not a common cause of unilateral epidural blockade. Anesth Analg 1990;71: 427–9.

In Response:

We thank Drs. Asato and Goto for their comments on our recent case report (1).

Their interpretative hypothesis of the dislocation of the catheter tip into the anterior epidural space is quite interesting but, in our opinion, it does not apply to the clinical case we have observed on the grounds of the following considerations:

1. If the bolus injection of bupivacaine through the needle had caused the bilateral spread of the anesthetic solution, a bilateral motor and sympathetic block of some degree would have appeared. The 12 mL, together with the test dose of 3 mL injected before, constitutes the 75% of the total anesthetic solution administered to the patient.
2. The previous attempt of epidural anesthesia, made with a bolus injection of 12 mL of 0.5% bupivacaine through the Tuohy needle, failed because unilateral sensory and motor block occurred.
3. Indeed, an epidurographic examination in the lateral view had been made, but the lack of radiopacity of the catheter did not allow us to better define the position of the tip in the epidural space; in addition, the radiogram did not seem to support an exclusive or prevalent distribution of the dye on the anterior side of the epidural space.

In conclusion, we think the occurrence of catheter tip misplacement into the anterior compartment of the epidural space is possible, as experimentally documented (2). Nevertheless, we would like to emphasize that even if this had occurred, we could not explain the lack of a bilateral motor and sympathetic block of some degree after 75% of

the total dose of anesthetic solution had been injected through the Tuohy needle without admitting the presence of a median fold of the dura mater in the epidural space.

Vito A. Peduto, MD
Riccardo Tani, MD
Luciana Marinelli, MD
Sergio Pani, MD
Institute of Anesthesia and Intensive Care
University of Cagliari, School of Medicine
Ospedale S. Giovanni di Dio
Via Ospedale, 09124 Cagliari
Italy

References

1. Peduto VA, Tani R, Marinelli L, Pani S. Bilateral analgesia and unilateral paresis after lumbar epidural blockade. Anesth Analg 1992;74:294–6.
2. Usubiaga JE, Dos Reis A, Usubiaga LE. Epidural misplacement of catheters and mechanisms of unilateral block. Anesthesiology 1970;32: 158–61.

Reinserting a Catheter Into a Single-Use Adapter: An Unsafe Method

To the Editor:

Kirchhoff and Stillwell (1) described a method of reinserting a catheter into a single-use adapter of a Continuous Spinal Anesthesia Tray (Kendall Healthcare Products Company, Mansfield, Mass.). They insert a sterile 22-gauge spinal needle retrograde through the silicon bushing. The stylet is then removed and the catheter is passed into the needle. The needle is removed, and the fitting is tightened again to secure the catheter.

However, the adapter is not sterile anymore after its inadvertent disconnection, and it is a dangerous practice to reinsert the same adapter. The "cost of opening a new tray can be avoided," but the cost of introducing some microorganisms into the spinal space cannot be calculated.

This problem was reported before (2), and the solution given was to use another adapter from the Portex Epidural Minipack, which also fits a smaller diameter catheter. Another solution is to use another sterile adapter that is separately packaged and supplied by Kendall Healthcare Products Company (3).

Joseph Eldor, MD
Department of Anesthesiology
Hadassah Medical Center, Ein Karem
P.O. Box 12142
Jerusalem 91120
Israel

References

1. Kirchhoff G, Stillwell R. Reinserting a catheter into a single-use adapter: a safe and cost-effective method. Anesth Analg 1991;73:826.
2. Eldor J, Gozal Y, Guedj P. An adapter for a microcatheter. Anaesthesia 1990;45:1098.
3. Wendell A. Adaptors for micro-catheters. Anaesthesia 1991;46:896.

In Response:

I wish to thank Dr. Eldor for indicating the lack of sterility of using an adapter (1). However, it is necessary to illustrate that both the catheter and adapter become contaminated. Consequently, there is still the miscalculated cost of introducing microorganisms into the spinal space with his suggested method. Perhaps it is more prudent to remove the catheter and replace the whole system.

Gary T. Kirchhoff, MD
Department of Anesthesiology
College of Medicine
University of South Florida
12901 Bruce B. Downs Boulevard, MDC 59
Tampa, FL 33612-4799

References

1. Eldor J, Gozal Y, Guedj P. An adapter for a microcatheter. Anaesthesia 1990;45:1098.

Contralateral Anesthesia Following Interscalene Block

To the Editor:

We would like to describe an unusual but potentially serious complication of interscalene approach to brachial plexus block.

A 33-yr-old, moderately obese (height 168 cm, weight 118 kg), "short necked," but otherwise healthy gentleman was admitted for right distal clavicle resection. An interscalene brachial plexus block was performed as described by Winnie (1). Forty-five milliliters of 1.5% mepivacaine with epinephrine (1:200,000) and sodium bicarbonate (1:10 by volume) was injected following an elbow paresthesia. Good right arm and shoulder motor and sensory block was achieved; the patient was sedated with 3 mg of midazolam, and surgery was started.

Forty-five minutes after the injection of mepivacaine, the patient complained of numbness of his left hand. Brief examination "under the drapes" revealed numbness and weakness in the left hand and arm. This progressed to a C-5 to T-8 sensory block on the left side, decreased motor function in the left arm (decreased triceps strength, very weak hand grip), and bilateral Horner's syndrome. The patient remained pain-free and had excellent muscle relaxation on the operative side. He was able to communicate in whisper only, could not cough, but was in no apparent distress. No changes in vital signs or oxygen saturation were noted. The surgery concluded uneventfully. In the recovery room (1 h 45 min after injection), the patient was found to have a vital capacity of 2100 mL, and neurologic examination remained unchanged from that in the operating room. The block started to dissipate 2 h 45 min after the injection in the following order: left motor, left sensory, left Horner, right motor, right sensory, and right Horner. By 3 h 40 min after the injection, the patient had no signs of block, with the return of normal voice and ability to cough.

Considerable speculation exists about the possible mechanism of contralateral anesthetic spread. Some suggest spread via the epidural space (2,3). Others (4) consider diffusion by the prevertebral fascial planes more likely and point out the slight risk of bilateral phrenic nerve block. Lombard and Couper (5) found a midline connective tissue septum behind the prevertebral fascia in cadavers. They

hypothesize its inadequate development in some individuals, allowing anesthetic spread across the midline. Possibility of diffusion via fascial planes to the contralateral side is supported by a report of a contralateral Horner's syndrome after stellate ganglion block (6).

The mechanism of the bilateral spread of anesthetic following interscalene brachial plexus block is unclear. Absence of significant hemodynamic changes and the sequential spread and regression of the block might favor the perifascial diffusion theory over epidural spread in our case. The route nonwithstanding, it is worrisome because of the potential for unilateral or bilateral recurrent laryngeal and phrenic nerve dysfunction and bilateral sympathetic block, as evidenced in our case by whisper, inability to cough, decreased vital capacity, and bilateral Horner's syndrome. One might be concerned about contralateral spread leading to bilateral phrenic and accessory muscle (intercostals, scalene) involvement with respiratory compromise, especially as ipsilateral phrenic nerve palsy occurs in virtually 100% of cited cases (7). This is why everyone having interscalene block, particularly obese people, people suffering from sleep apnea, patients with a "difficult airway," with pulmonary disease, or simply heavily sedated, should be monitored especially carefully.

Edward Gologorsky, MD
Raymond F. Leanza, MD
Department of Anesthesiology and Critical Care Medicine
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15261

References

1. Winnie AP. Interscalene brachial plexus block. Anesth Analg Curr Res 1970;49:455–66.
2. Kumar A, Battit GE, Froese AB, Long MC. Bilateral cervical and thoracic epidural blockade complicating interscalene brachial plexus block: report of two cases. Anesthesiology 1971;35:650–2.
3. Huang KC, Fitzgerald MR, Tsueda K. Bilateral block of cervical and brachial plexuses following interscalene block. Anaesth Intensive Care 1986;14:87–8.
4. Cobcroft MD. Bilateral spread of analgesia with interscalene brachial plexus block. Anaesth Intensive Care 1976;4:73.
5. Lombard TP, Couper JL. Bilateral spread of analgesia following interscalene brachial plexus block. Anesthesiology 1983;58:472–3.
6. Allen G, Samson B. Contralateral Horner's syndrome following stellate ganglion block (letter). Can Anaesth Soc J 1986;33:112–3.
7. Urmey WF, Talts KH, Sharrock NE. One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 1991;72:498–503.

Ventilatory Depression and Midazolam

To the Editor:

The excellent article by Alexander et al. (1) answers the important clinical issue as to whether more ventilatory depression is produced by bolus or constant infusion of midazolam. The data show that slow administration of midazolam produces no independent protection from respiratory depression, which is a function of total dose rather than speed of injection.

Even though the final sentence of the article mirrors my own personal prejudices, I believe that the data presented do not support the first portion of the conclusion. ("Rather, the present data suggest that midazolam should be administered in small, incremental doses; the decision to administer additional midazolam should be delayed for 2–3 min, until the respiratory depressant effects of previous doses have reached their peak.") The data as expressed in Figure 4 do show that 2–3 min are required until maximal respiratory depression can be observed whether the dose is given as a bolus or 5-min infusion. However, none of the data presented show that less depression is encountered by small incremental doses of midazolam. The appropriate conclusion regarding dosing that should be derived from the data is that 0.1 mg/kg IV midazolam is well tolerated in healthy subjects whether given over 15 s or 5 min.

William W. Pond, MD
Michael Hartman, DVM
Fort Wayne Center for Medical Education
Indiana University School of Medicine
Fort Wayne, Indiana

Reference

1. Alexander CM, Teller LE, Gross JB. Slow injection does not prevent midazolam-induced ventilatory depression. Anesth Analg 1992;74:260–4.

In Response:

We appreciate the comments by Drs. Pond and Hartman regarding our recent article (1). We did not intend to imply that a given dose of midazolam, administered incrementally, causes less ventilatory depression than the same *total* dose of midazolam administered over a few seconds. Rather, our recommendation was that midazolam be administered incrementally, so that each patient's total midazolam dose can be individualized. This "titration" requires that the effect of each incremental dose be assessed before further midazolam is given. Our data suggest that for maximal safety, subsequent doses of midazolam should be given no sooner than 2 min after the *end* of the previous dose. Slow infusion offers no advantage over rapid administration of these incremental doses; in fact, it will increase the time that must elapse before the full respiratory depressant effect of each dose becomes apparent.

Finally, our subjects' ventilation was continuously stimulated by CO_2, and their F_{IO_2} always exceeded 50%. Therefore, one must not extrapolate from our data that a single dose of midazolam (0.1 mg/kg IV), by bolus injection or infusion, is appropriate for all healthy subjects. The key words for the safe use of midazolam are START LOW and GO SLOW.

Christian M. Alexander, MD
Lynn E. Teller, MD
Department of Anesthesia
University of Pennsylvania

Jeffrey B. Gross, MD
Department of Anesthesiology
University of Connecticut
Farmington, CT 06030

Reference

1. Alexander CM, Teller LE, Gross JB. Slow injection does not prevent midazolam-induced ventilatory depression. Anesth Analg 1992;74:260–4.

Interpleural Regional Analgesia—A Simple Cause of Catheter Obstruction

To the Editor:

Interpleural regional analgesia for pain relief after surgery is simple, safe, and effective (1,2). We have successfully used this technique as a method of analgesia in 18 post-cholecystectomy patients. However, in our experience we have encountered two instances of failure to administer a top-up dose via the catheter. In both these patients, an interpleural catheter (Arrow Interpleural Anesthesia Set) was successfully inserted percutaneously using the saline infusion technique (3). After attachment of the catheter adaptor and bacterial filter, an initial dose of bupivacaine was easily injected into the pleural cavity. Administration of the next top-up dose was uneventful in both patients. However, during the administration of a subsequent top-up dose, absolute resistance to bupivacaine injection was noticed. On examination of the catheter adaptor and the filter unit, it was observed that the catheter had collapsed at the point where the adaptor held it in place. Cutting off this portion and reattaching the catheter to the adaptor and bacterial filter restored its patency as shown by subsequent easy injection of the local anesthetic.

The above instances illustrate that routinely the catheter material withstands the compressive force of the adaptor well but over time, in an occassional case, it may collapse producing obstruction. Thus, we would advocate that the adaptor end of the catheter should be checked first in cases of catheter obstruction before the catheter is removed from the patient.

Mohammad Maroof, MD
Mahmood Siddique, MD
Rashid M. Khan, MD
Department of Anesthesiology
King Fahad Hospital
P.O. Box 22490, Riyadh 11426
Saudi Arabia

References

1. Reiestad F, Stromskag KE. Interpleural catheter in the management of post-operative pain: a preliminary report. Reg Anesth 1986;11:89–91.
2. Reiestad F, Stromskag EK, Holmqvist E. Intrapleural administration of bupivacaine in post-operaitve management of pain. Anesthesiology 1986; 65:A204.
3. Scott PV. Interpleural regional analgesia: detection of the interpleural space by saline infusion. Br J Anaesth 1991;66:131–3.

Anesthetic Management in Charcot-Marie-Tooth Disease

To the Editor:

Greenberg and Parker (1) correctly address some of the concerns regarding anesthesia in patients with Charcot-Marie-Tooth disease (CMTD). One unresolved issue is the possible danger of succinylcholine in a disease characterized by muscular denervation. We recently completed a retrospective survey of 86 patients with CMTD who underwent 161 surgical procedures (2). Forty-one of these patients received succinylcholine on 56 occasions. Despite the fact that denervation poses the greatest risk for hyperkalemia from succinylcholine (3), no complications occurred from its use. Presumably, muscular atrophy in CMTD occurs faster than the denervation process so that the amount of sensitive muscle is relatively small. Related to this, no complications appeared to have occurred in those patients who received nondepolarizing muscle relaxants. However, individuals who have acute exacerbations of their disease, such as the one described by Brian et al. (4), may represent a subset of patients who might have altered responses to muscle relaxants. Thus, during acute exacerbations, succinylcholine should probably be avoided and other muscle relaxants used with appropriate neuromuscular monitoring.

Last, I would like to inform your readers of the existence of CMT International, an organization dedicated to helping people with CMTD. A research and medical advisory board is available to answer any questions regarding CMTD. The address and phone number are One Springbank Drive, St. Catharines, Ontario, Canada L2S 2K1, (416) 687-3630.

Joseph F. Antognini, MD
Department of Anesthesiology
University of California, Davis
School of Medicine, TB-170
Davis, CA 95616-8634

References

1. Greenberg RS, Parker SD. Anesthetic management for the child with Charcot-Marie-Tooth disease. Anesth Analg 1992;74:305–7.
2. Antognini JF. Anaesthesia for Charcot-Marie-Tooth disease: a review of 86 cases. Can J Anaesth 1992;39:398–400.
3. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.
4. Brian JE, Boyles GD, Quirk JG, Clark RB. Anesthetic management for cesarean section of a patient with Charcot-Marie-Tooth disease. Anesthesiology 1987;66:410–2.

In Response:

We appreciate Dr. Antognini's comments regarding our case report and suspect that he is correct regarding the safety of depolarizing muscle relaxants in the majority of patients, with the possible exception being those with an acute exacerbation of their neuromuscular disease. This may be particularly important in patients with underlying conditions that may alter the response to muscle relaxants, such as pregnancy. Accordingly, one's clinical decision-making should be based on the risk (probably minimal) of using succinylcholine versus the need to obtain immediate control of the airway. In many cases, as in our report, the use of an intermediate-acting nondepolarizing muscle relaxant represents a viable alternative.

We are surprised and delighted to learn of CMT International and would hope that interested persons take advantage of its expertise.

Robert S. Greenberg, MD
Stephen D. Parker, MD
Department of Anesthesiology and Critical Care
The Johns Hopkins Hospital
600 North Wolfe Street
Blalock 1410
Baltimore, MD 21205

Section Editor
Norig Ellison

Book Reviews

Drugs for the Heart

L. H. Opie, ed. Philadelphia: W. B. Saunders, 1991, 302 pp, $24.95.

Drugs for the Heart summarizes the full breadth of cardiovascular pharmacology in a compact, concise format. The book is organized by class of drug: β-blocking agents, nitrates, calcium channel antagonist, diuretics, ACE inhibitors and vasodilators, digitalis and other inotropes, antihypertensives, antiarrhythmics, etc. Dr. Opie has assembled an authoritative, international group of cardiologists to assist in the preparation of this book while remaining a coauthor for each chapter. Therefore, the book benefits from a unified writing style while still being remarkable for the currentness of its references. His clear illustrations complement the discussions throughout. These copyrighted, line drawings are one of the book's unique assets; and, by themselves, may justify its acquisition for many readers. Most chapters are also complemented by concise tables summarizing the most important aspects of the drugs' pharmacology. The authors' wise use of both generic and trade names adds greatly to the convenience of this book (patients often only know the trade name of their medications). The authors have not limited their discussions to drugs currently approved by the U.S. Food and Drug Administration, but also cover medications in use in Europe, many of which will undoubtedly find their way into American practice in the near future.

Cardiovascular pharmacology has evolved dramatically over the past decade. Entire new classes of agents have emerged and become central to the care of the patient with cardiovascular disease. Dozens of new drugs have been introduced, and busy anesthesiologists may have difficulty keeping track of this myriad of medications. Many may find a quick reference to this book during preoperative evaluation extremely useful. It should be emphasized that *Drugs for the Heart* does not deal with anesthetic considerations per se. However, the concise coverage of the drug's clinical pharmacology will be adequate for most anesthesiologists, who can then deduce the anesthetic implications for themselves.

With its unusual size (4 3/4 in. × 10 in.), *Drugs for the Heart* is designed to be carried in the pocket of a lab coat for convenient reference. Trainees will probably carry this book during their critical care rotations. Others in anesthesia may not wish to devote a pocket to the book, but rather will keep it on their desk (or in a locker) for ready reference. This gem of a book should also be available in departmental libraries and anesthesia "preop" clinics.

R. K. Baumgarten, LT COL, MC
Brooke Army Medical Center
San Antonio, Texas

New Developments in Pediatric Anesthesia

Volume 9, No. 4 of Anesthesia Clinics of North America

Jerrold Lerman, ed. Philadelphia: W. B. Saunders, 1991, 219 pp, $74.00 annual subscription or $32.50 for single issue.

The great value of this monograph lies in its timeliness. Intermediary in production lag between journal articles and textbook chapters, the entries in this volume offer recently generated information of interest and value to everyone caring for children in settings ranging from tertiary-care hospitals to ambulatory-surgery centers.

The topics were selected by the editor precisely because new research, new drugs, and new insights have altered the practice of pediatric anesthesia, enhancing safety and allaying anxiety in a population exceedingly vulnerable to trespass upon the body and the spirit. In his preface, the editor states that the mandate to the authors was to review the current understanding of their subjects, and then discuss the relevance of recent advances to pediatric anesthesia. The authors have succeeded admirably: the entries are clear, succinct, well-cited, and indeed clinically relevant.

The contents reflect advances in pharmacology, preoperative preparation, monitoring, intraoperative management, and pathophysiology. Some, like "Congenital Diaphragmatic Hernia" by Bohn, unfold with all the drama and suspense of a good detective story as the reader is guided through the evolution of our understanding of the pathophysiology of diaphragmatic hernia and the attendant progress in its management. Others, like "Opioids in Pediatric Anesthesia and in the Management of Childhood Pain" by Yaster, Nicholas, and Maxwell, "Postoperative Pain Management for Children" by Goresky, Klassen, and Waters, and "Regional Anesthesia" by Hannallah offer practical information in the long-neglected area of treatment of pediatric pain. The chapters "Preoperative Fasting and Medication in Children" by Morrison and Lockhart, "Pharmacokinetics and Pharmacodynamics of Inhalational Anesthetics in Infants and Children" by Lerman, and "Neuromuscular Blocking Drugs" by Brandom are excellent in their discussion of the differences between adults and children (and among neonates, infants, and children) for the newer and the more familiar drugs.

New thoughts on the pathophysiology and management of respiratory and metabolic derangements peculiar to children are addressed by Welborn in "Perioperative Apnea in the Preterm Infant" and Ryan in "Malignant Hyperthermia: Treatment and After Care." These articles dove-tail well with the contributions "Oximetry and Capnography Monitoring" by Badgwell and "Body Temperature and Anesthesia" by Bissonnette. All discussions of

©1992 by the International Anesthesia Research Society

drugs, physiology, and monitoring are complemented by the absolutely superb work by Cote, "Blood, Colloid, and Crystalloid Therapy." Having done much of the cited research himself, his treatment of the topic is thorough and his advice well-substantiated, practical, and easy to implement. This article alone is definitely worth the price of the monograph.

On the minus side, it is a pity that some of the articles in this well-written, well-documented, useful volume are marred by textual imperfections including typographical errors, misspellings, word substitutions, and other sloppiness. Additionally, the type size of the text is *very* small—smaller than the type in which the Foreward, Preface, and Contents are set. As the people who may benefit the most from this volume are those whose abilities to read the fine print are diminishing, the editors and publisher might consider using the next larger point size, perhaps with less "lead" or white space between the lines.

All-in-all, *New Developments in Pediatric Anesthesia* not only accomplishes its goal of demonstrating the relevance of the new developments in pharmacology, physiology, and monitoring to pediatric anesthesia, but does so in a scholarly, practical, and eminently readable fashion. Dr. Lerman and his authors are to be commended for this contribution to the libraries of trainees and practitioners alike.

Philippa Newfield, MD
California Pacific Medical Center
San Francisco, California

A Glance at Transesophageal Echocardiography

R. A. Gal. New York: Churchill-Livingstone, 1992, $95.00.

This teaching videotape on transesophageal echocardiography (TEE) has been prepared for cardiologists, anesthesiologists, and radiologists. The videotape runs for 100 minutes and consists of two parts. The first part covers TEE equipment, the TEE examination in the conscious patient, and some standard TEE views of the heart and aorta. The second part uses 50 case illustrations to demonstrate the role of TEE in the diagnosis of cardiovascular pathology. There are sections on native and prosthetic valvular disease, tumors, embolic disease, infective endocarditis, congenital heart disease, aortic pathology, coronary heart disease, interventional procedures (including intraoperative aspects), and the critically ill patient.

The major strengths of this videotape presentation are the author's obvious experience with TEE, the number and diversity of case illustrations, and the fine blend of video and superimposed dialogue that is often achieved.

The deficiencies are more numerous, however. The author assumes some knowledge of echocardiography and does not set out to teach the basics. If this is the case, then the introductory sections on transesophageal equipment and the examination are superfluous. For an inexperienced viewer, the section on standard views is too brief and barely touches on the longitudinal imaging plane that is now widely available with biplane TEE. To appreciate this videotape, the viewer needs to have a solid grounding in the fundamental principles of echocardiography with a good working knowledge of two-dimensional, M-mode, quantitative and color flow Doppler, and some background exposure to conventional transthoracic echocardiography. Few anesthesiologists will have this background; if they do, they will find the emphasis on diagnostic curios largely irrelevant. The case illustrations relevant to an anesthesiologist's practice, e.g., abnormalities of global and regional left ventricular function, are scattered amongst the many examples and do not fall into a discrete subsection. Often the pathological description is either too superficial or lacks precision. For example, in describing mitral stenosis (case 1) the author makes no attempt to describe the valve leaflets or type of deformity. Alluding to the risk of pulmonary thromboembolism from a large thrombus attached to a central venous catheter, the author states ". . . the mobility of the thrombus looks really very impressive" (case 18). The organization of the individual case illustrations is often haphazard and the time allotted to them is frequently disproportionate to their importance. For example, more than 8 minutes is devoted to a single case of infective endocarditis leading to aortic root abscess (case 19), whereas only 5 minutes is allotted to four cases depicting native valvular disease (cases 1–4). The questionable clinical judgment relative to some of the cases discussed in this videotape presentation, despite the author's disclaimer, results in a rather confusing picture of the true indications for and value of TEE.

This videotape presentation will be of interest to cardiologists who have little experience with the relatively new modality of TEE. It will be of little value, however, to the anesthesiologist interested in monitoring patients at high risk of cardiac morbidity in the operating room.

Martin D. Abel, MD
Mayo Medical School
Rochester, Minnesota

Dripps/Eckenhoff/Vandam Introduction to Anesthesia, 8th edition

D. E. Longnecker and F. L. Murphy, eds. Philadelphia: W.B. Saunders, 1992, 495 pp, ISBN 0-7216-3525-3.

This is the eighth edition of this venerable introductory anesthesia text which began as a manual for anesthesia house staff and was first published by Dripps, Eckenhoff, and Vandam in 1956. Like the specialty this book introduces, it has undergone many changes and increased considerably in size and complexity during the intervening years. The new, larger, two-column format is easy on the eyes. The seventh edition was authored mainly by the faculty at Northwestern University. This new edition is almost exclusively a product of the University of Pennsylvania anesthesia faculty and the number of contributors has nearly doubled.

The contents of the volume are rationally divided into seven sections beginning with Fundamentals and Preparation and concluding with Post Anesthetic Care. A major portion of the book is devoted to patients with special requirements and focuses more on the problems presented by such patients than the more conventional, and less

satisfactory, grouping according to anesthesia subspecialties. There are new chapters devoted to the management of patients with hepatic and renal disease and those with metabolic and endocrine disorders. There is also an excellent chapter on the positioning of the surgical patient. The final chapter entitled "The Further Study of Anesthesiology" provides some excellent advice for the resident beginning the first year of training. The text is supported by clear and well-labeled illustrations. Each chapter has a brief but carefully selected bibliography.

It is the reviewer's prerogative to engage in nit-picking. It is distressing to find that the discussion of the anesthesia record had shrunk from a six-page chapter to a half-column paragraph in this edition. In view of the importance of the record and the lack of care that a great many anesthesiologists devote to it, this seems unjustified. Despite this minor shortcoming, the editors have done an excellent job in producing an accurate, concise, well-documented and highly readable text that is remarkably well integrated considering the multiplicity of contributors.

In summary, the *Dripps/Eckenhoff/Vandam Introduction to Anesthesia* has been the premiere beginners' text since its inception some 35 years ago. This new eighth edition certainly fulfills its editors' promise "to reflect current anesthesia practice" and should continue to generate its well-deserved popularity with medical students, beginning anesthesia residents, and those physicians in other specialties who require a survey of the field.

Martin Helrich, MD
University of Maryland School of Medicine
Baltimore, Maryland

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Bready LL, Smith RB. *Decision Making in Anesthesiology*. 2nd ed. St. Louis: Mosby Year Book, 1992, 410 pp, $59.00, ISBN 1-55664-344-6.

Bodman R, Gillies D. *Harold Griffith. The Evolution of Modern Anesthesia*. Toronto: Hannah Institute, 1992, 128 pp, ISBN 1-55002-155-9.

Brown DL, ed. *Risk and Outcome in Anesthesia*. 2nd ed. Philadelphia: J.B. Lippincott, 1992, 606 pp, $79.50, ISBN 0-397-51134-5.

Mostafa SM, ed. *Anaesthesia for Ophthalmic Surgery*. New York: Oxford Medical Publications, 1991, 338 pp, $80.00, ISBN 0-19-261960-8.

Oka Y, Goldiner PL, ed. *Transesophageal Echocardiography*. Philadelphia: J.B. Lippincott, 1992, 338 pp, $150.00, ISBN 0-397-51158-2.

Sandler AN, ed. *Current Concepts in Acute Pain Control*. Volume 10, No. 2 in Anesthesiology Clinics of North America, Philadelphia: W.B. Saunders, 239 pp, $78.00 annual subscription or $32.00 single issue, ISSN 0889-9537.

Stanley TH, Sperry RJ, eds. *Anesthesia and the Lung 1992*. Volume 25 in Critical Care Medicine and Anesthesiology. Boston: Kluwer Academic Publishers, 1992, 329 pp, $68.00, ISBN 0-7923-1563-4.

Vitez TS, ed. *Quality Improvement Systems and Anesthesia*. Volume 30, No. 2 of International Anesthesiology Clinics, Boston: Little Brown & Company, 1992, 128 pp, $81.00 annual subscription, ISSN 0020-5907.

Woerbe GM. *Kinetics and Dynamics of Intravenous Anesthetics*. Volume 26 in Critical Care Medicine and Anesthesiology. Boston: Kluwer Academic Publishers, 1992, 253 pp, $103.00, ISBN 0-7923-1506-5.

Ochsner

ANESTHESIOLOGIST OPENINGS

Positions are available at the Ochsner Clinic New Orleans and Ochsner Clinic Baton Rouge for BC/BE anesthesiologists.

Ochsner Clinic New Orleans:

- Generalists
- Intensivist Medical Director for 32-bed medical surgical ICU

Ochsner Clinic Baton Rouge:

- Generalists
- Pain
- Critical Care

Ochsner offers a very competitive salary, rich fringe benefits package, two substantial retirement programs, excellent paid vacation and CME time, all malpractice insurance provided, and opportunity for partnership status. Send CV to:

Ochsner Clinic
16777 Medical Center Drive
Reference #A1ANES
Physician Recruiting Support Services
Baton Rouge, LA 70816
1-800-488-2240

A.S.I.A.
AMERICAN SOCIETY OF INDIAN ANESTHESIOLOGIST
PRESENTS

"CURRENT ISSUES IN ANESTHESIA"
Place: The Showboat Hotel and Casino
Atlantic City

Friday, Saturday, and Sunday
SEPTEMBER 11, 12 AND 13, 1992

Topics	Speakers
The Role of Neurolytic Procedures in Pain Management	Subhash Jain, M.D.
Recent Advances in OB Anesthesia	Sivam Ramanathan, M.D.
Anesthesia for Major Vascular Surgery	Ketan Shevde, M.D.
Controversies in Ambulatory Surgery	Surinder Kallar, M.D.
Implementation of RBRVS: Challenges and Opportunities	Jody Locke, Datamedic
Partnerships, P.C.s and Contracts	Jeffrey Slavet, Esq. & Anthony Mustalish, M.D.
Innovative Airway Management	Vijayalakshmi Patil, M.D.
Fiberoptic Intubation	Adranik Ovassapian, M.D.
Hands On Demonstration: Fiberoptic Scope	Adranik Ovassapian, M.D.

There will be a **RECEPTION, GALA DINNER** plus **ENTERTAINMENT** at the Showboat Hotel on Saturday, September 12, 1992 at 8:00 pm for registrants and their families. It promises to be an excellent conference for both an educational and recreational point of view. A block of rooms has been reserved at the Showboat Hotel, Atlantic City, New Jersey. For registration material and additional information contact: ASIA P.O. Box 44-1353, Somerville MA, 02144 PH. (617) 628-0020, FAX (617) 666-5180 Attn: Narendra Shah, M.D. **For Hotel and Flight reservations: World Wing Travel and Tours PH (212) 736-9630, FAX (212) 594-9030. CME CREDIT AVAILABLE**

The Changing Practice of Anesthesia

DEPARTMENT OF ANESTHESIA
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

GRAND HYATT, SAN FRANCISCO, CALIFORNIA
SEPTEMBER 17-20, 1992

TOPICS INCLUDE:

- **Pediatrics**
- **New Drugs and Technologies**
- **Neuroanesthesia**
- **Obstetrics**
- **Critical Care/Economics/Ethics**
- **Ambulatory Anesthesia**
- **Controversies in Clinical Management**
- **Regional Anesthesia/Pain Management**
- **Cardiac Update**
- **AIDS/Transfusion Practices**

PROGRAM FACULTY: members of University of California, San Francisco, School of Medicine

Course Registration *The Changing Practice of Anesthesia*
Mail to: San Francisco General Hospital
Anesthesia Research Foundation
Attention: Karen Sitland
1001 Potrero Avenue, Room 3S-50
San Francisco, CA 94110

For program information, please contact Karen Sitland at (415) 206-8145.

Registration Information:
(415) 206-8145; Office hours 9:00 a.m. to 4:00 p.m. PDT

Name _____

Address _____

City _____ State _____ Zip _____

Telephone ( ) _____

Registration fee (please check)
(Fee includes course materials, Friday lunch, and wine reception at the Grand Hyatt)

Before September 1, 1992

❑ Physicians $385 ❑ C.R.N.A. $285 AANA #_____

❑ Residents, Interns & Student Nurse Anesthetists $185
(include a letter from program director)

After September 1, 1992

❑ Physicians $395 ❑ C.R.N.A. $295 AANA #_____

❑ I cannot attend, please send a syllabus. Enclosed is $35.

Make check payable to: **Anesthesia Research Foundation**

Refund Policy:
There will be a service charge of $30 withheld from all registration fees. No refunds will be given after the program begins.

ANESTHESIA INTENSIVISTS

UMDNJ, New Jersey's university of the health sciences, is recruiting for two Anesthesia Intensivists for the Department of Anesthesia to be Co-Directors of the Surgical Intensive Care Unit at Robert Wood Johnson University Hospital. This 20 station modern unit is expanding to 27 stations in our 416 bed tertiary care facility, located in Central New Jersey. Academic rank and salary will be commensurate with qualifications.

Send cover letter, CV, and 3 letters of reference to: **Sanford L. Klein, D.D.S., M.D., Chairman, Department of Anesthesia, UMDNJ - Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place, CN 19, New Brunswick, NJ 08903-0019.** UMDNJ, New Jersey's university of the health sciences, is an Affirmative Action/Equal Employment Opportunity Employer, m/f/h/v, and a member of the University Health System of New Jersey.

UMD NEW JERSEY

Medical Director, Ambulatory Surgery Center

The Mercy Hospital of Pittsburgh is searching for a Medical Director of a new Ambulatory Surgery Center. Interested candidates must be board certified in Anesthesiology or Surgery. Candidates must have at least three years' experience in clinical anesthesia or surgery and in administration of an Ambulatory Surgery Center. Mercy Hospital is a 524-bed advanced teaching and referral center serving a tri-state area with an extensive surgical program and separate Ambulatory Surgery Center.

Submit curriculum vitae in confidence to:

Irene McFadden, Vice President
Ambulatory & General Services
Mercy Hospital of Pittsburgh
1400 Locust Street
Pittsburgh, PA 15219

Applications will be reviewed monthly until the position is filled.

E.O.E.

Mercy Hospital
The Mercy Hospital of Pittsburgh

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARDS

1993 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARDS

Applications for up to $25,000 are invited for the 1993 Awards, subject to the following basic conditions:

- Proposals must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- Applicants must be members of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 11, 1992. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
2 Summit Park Dr., #140
Cleveland, OH 44131
Telephone: (216) 642-1124

The 1993 Awards will be announced at the 67th Congress of the International Anesthesia Research Society to be held at the San Diego Marriott, March 19–23, 1993.

Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® 5 mg/mL Injectable

(diltiazem hydrochloride)

BOLUS | INFUSION



GAINS HEART RATE CONTROL QUICKLY...

CIVAH495/A8113

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAH495/A8113

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action from first bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1†]
- Do not use in Af/Fl patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome and second- or third-degree AV block except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see the brief summary of prescribing information on an adjacent page.

6493E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	If response is inadequate, wait 15 minutes	Treatment as
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

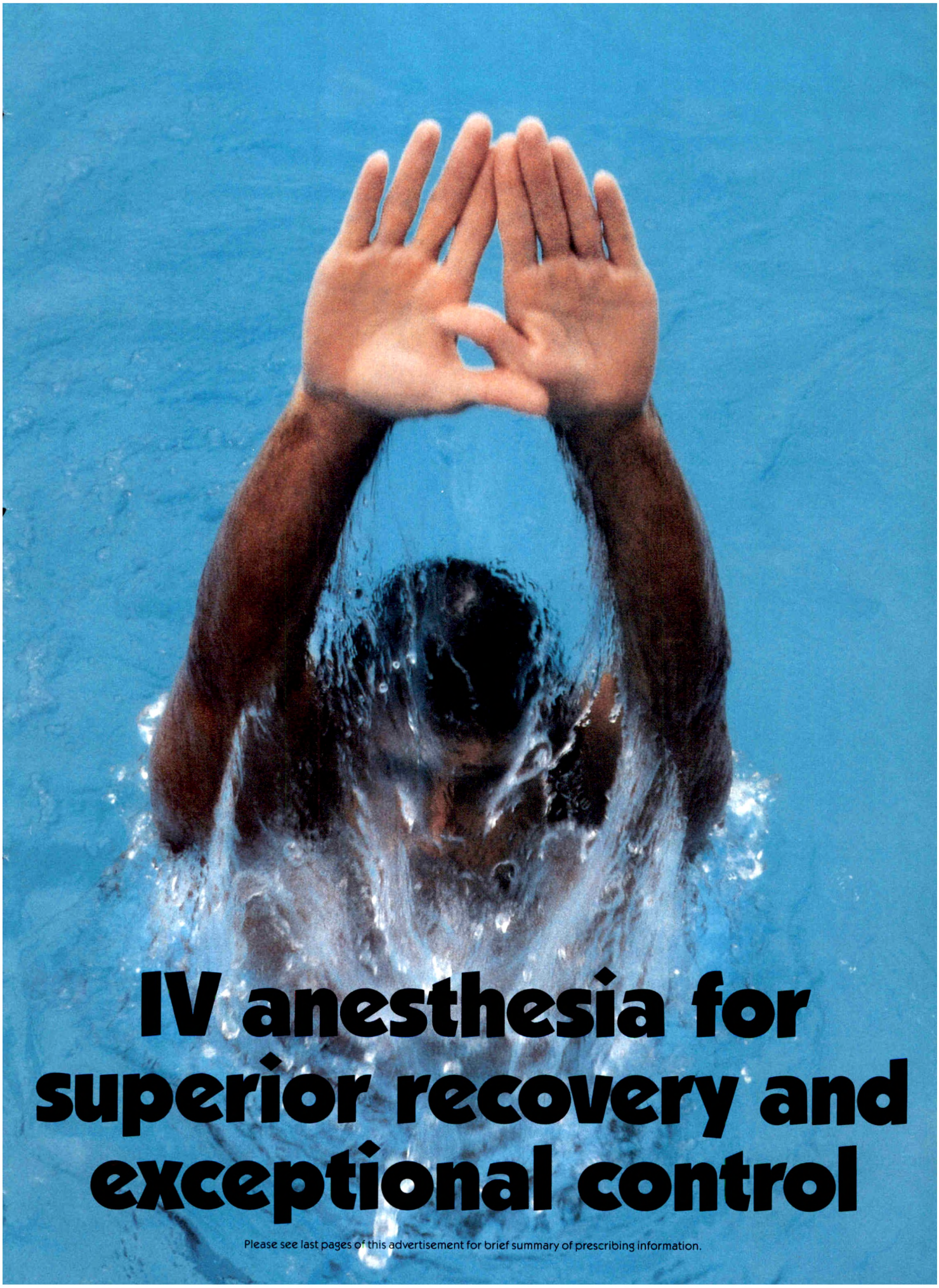
Product information as of October 1991

References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

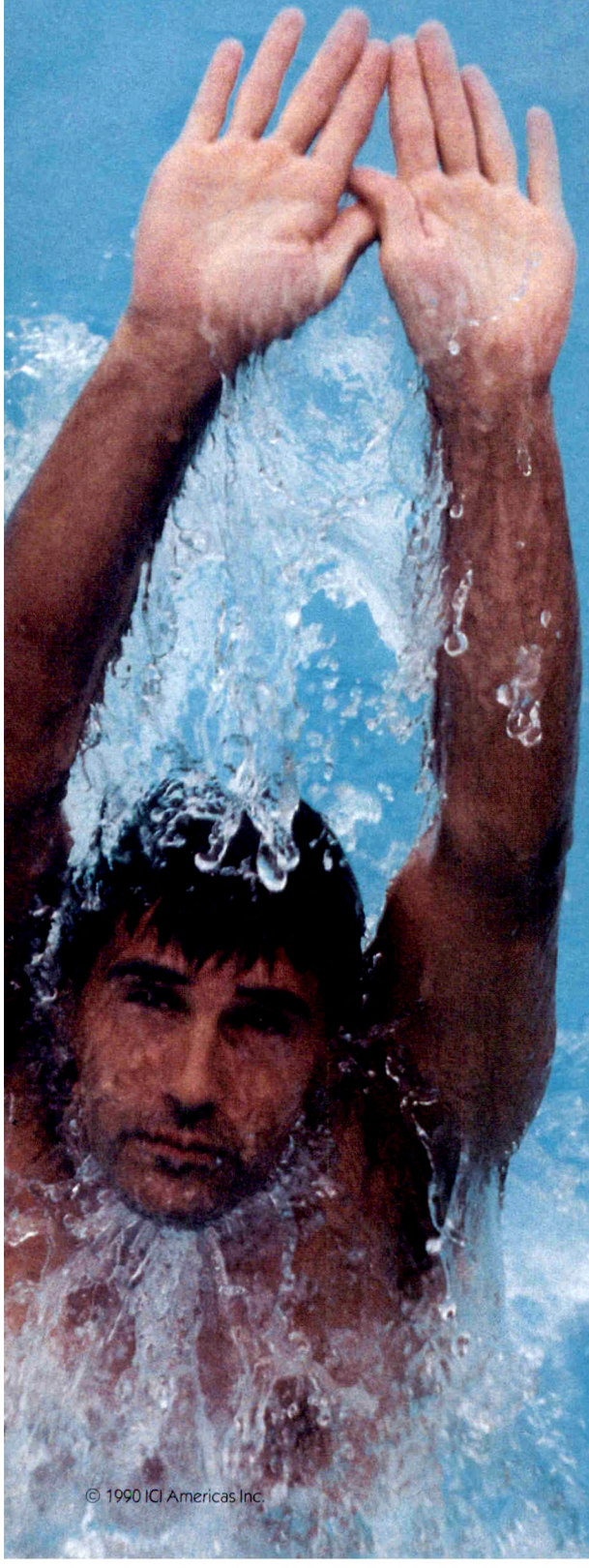
CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

CIVAH495/A8113 6493E2



Please see last pages of this advertisement for brief summary of prescribing information.

Superior exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

© 1990 ICI Americas Inc.

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

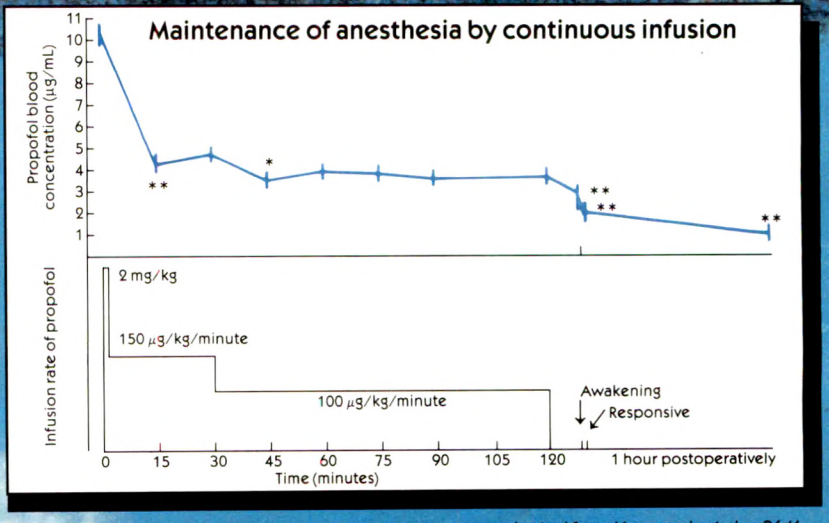
For induction and maintenance

DIPRIVAN®
INJECTION propofol

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)
After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μg/kg/min for 30 minutes—then 100 μg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

ecovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.†

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
†Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION propofol

For induction and maintenance

DIPRIVAN®

INJECTION *propofol*



Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN® (propofol) Injection

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert. A Brief Summary follows.)

CLINICAL PHARMACOLOGY – Individualization of Dosage: General: DIPRIVAN Injection is a potent sedative hypnotic agent which provides clinically useful anesthetic and sedative actions depending upon the dose and technique of administration. Important factors to consider include the types of preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient, and ultimately, the dose and rate of administration of DIPRIVAN Injection. Individualization of dose and technique will provide a smooth induction and stable maintenance while reducing potential unwanted side effects. Patients with hypovolemia should have fluid-volume deficits corrected prior to administration of DIPRIVAN Injection. **Induction of Anesthesia:** Most adult patients under 55 years of age and classified ASA I or II require 2.0 to 2.5 mg/kg of DIPRIVAN Injection for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injection. It is important to be familiar with and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated and ASA III or IV patients. Due to the reduced clearance and higher blood levels, most elderly patients require approximately 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN Injection for induction of anesthesia according to their condition and responses. A rapid bolus should not be used as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. (See DOSAGE AND ADMINISTRATION.) **Maintenance of Anesthesia:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, syringe pumps or volumetric pumps must be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 100 to 200 μg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction dose higher rates of infusion are generally required (150 to 200 μg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as an opioid, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. When supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN Injection and/or opioids should be increased in order to provide adequate anesthesia. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 50 to 100 μg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and opioid analgesics, as well as with inhalational and regional anesthetic agents. In the elderly, rapid bolus doses should not be used as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction and/or oxygen desaturation. Most elderly patients require a reduction of the recommended maintenance rates for healthy adults (< 55 years) to 50 to 100 μg/kg/min (3 to 6 mg/kg/h). **MAC SEDATION:** When DIPRIVAN Injection is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients the rates of DIPRIVAN Injection administration will be approximately 25% of those used for maintenance of general anesthesia. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus dose administration. In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) **A rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. Initiation of MAC Sedation:** For initiation of sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injection at 100 to 150 μg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the desired level of sedation while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injection is administered slowly over 3 to 5 minutes, most patients will be adequately sedated and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration should be over 3-5 minutes and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) **Maintenance of MAC Sedation:** For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance. Infusion rates should subsequently be decreased over time to 25 to 50 μg/kg/min and adjusted to clinical responses. In titrating to clinical effect, allow approximately 2 minutes for onset of peak drug effect. Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of DIPRIVAN Injection at rates higher than are clinically necessary. If the intermittent bolus dose method is used, increments of DIPRIVAN Injection 10 mg (1.0 mL) or 20 mg (2.0 mL) can be administered and titrated to desired level of sedation. With the intermittent bolus method of sedation maintenance there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) DIPRIVAN Injection can be administered as the sole agent for maintenance of MAC sedation during surgical/diagnostic procedures. When DIPRIVAN sedation is supplemented with opioid and/or benzodiazepine medications, these agents increase the sedative and respiratory effects of DIPRIVAN and may also result in a slower recovery profile. (See PRECAUTIONS, Drug Interactions.) **INDICATIONS AND USAGE:** DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection, when administered IV as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures. DIPRIVAN Injection may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation, in obstetrics including cesarean section deliveries, in nursing mothers, and in pediatric patients. **CONTRAINDICATIONS:** DIPRIVAN Injection is contraindicated in patients with a known hypersensitivity to DIPRIVAN Injection or its components, or when general anesthesia or sedation are contraindicated. **WARNINGS: For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. MAC sedation patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated and ASA III or IV patients. DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness. PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and ASA III or IV patients. (See CLINICAL PHARMACOLOGY – Individualization of Dosage.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. Accidental intra-arterial injection has been reported in patients, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. There have been reports of pulmonary edema in temporal relationship to the administration of DIPRIVAN Injection, although a causal relationship is unknown. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound, and/or asystole. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. There have been rare reports of cardiac arrest in temporal relationship to the administration of DIPRIVAN Injection. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following

DIPRIVAN® (propofol) Injection

DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion are prevented by appropriate measures. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of opioids and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia or sedation, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN Injection crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injection may be associated with neonatal depression. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from publications and marketing experience in over 8 million patients; there are insufficient data to support an accurate estimate of their incidence rates. The adverse experience profile from reports of 150 patients in the US/Canadian MAC sedation clinical trials is similar to the profile established with DIPRIVAN Injection during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea. The most common adverse events which occurred in more than 3% of the patients receiving DIPRIVAN Injection for MAC sedation included hypotension, nausea, headache, and injection site pain or hotness. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 2588 patients included in the US/Canadian studies. These studies were conducted using a variety of premedicants, varying lengths of surgical/diagnostic procedures and various other anesthetic/sedative agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1% – All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY). Bradycardia, Hypertension, Arrhythmia. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching. **Digestive:** Nausea** (15%), Vomiting*, Abdominal Cramping. **Injection Site:** Pain*, Burning/Stinging*. **Respiratory:** Hiccough, Cough (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Rash. Incidence of unmarked events is 1%-3%; *3% to 9%; **10% or greater. **Incidence Less than 1% – Causal Relationship Probable, derived from clinical trials.** (Adverse events reported in the literature, not seen in clinical trials, are *italicized*.) **Body as a Whole:** Perinatal Disorder, Extremities Pain, Awareness, Chest Pain, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain. *Anaphylaxis/Anaphylactoid Reaction.* **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Syncope, Premature Atrial Contractions, Abnormal ECG, ST Segment Depression, Bundle Branch Block, Extrasystole, Myocardial Infarction, Heart Block, Atrioventricular Block, Second Degree A-V Block. **Central Nervous System:** Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement, Hypertonia/Dystonia, Chills/Shivering, Somnolence, Tremor, Agitation, Confusion, Delirium, Paresthesia, Abnormal Dreams, Euphoria, Fatigue, Moaning, Rigidity, Combativeness, Depression. **Digestive:** Hypersalivation, Dry Mouth, Swallowing, Enlarged Parotid. **Injection Site:** Tingling/Numbness, Coldness, Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Metabolic/Nutritional:** Hyperlipemia. **Musculoskeletal:** Myalgia. **Respiratory:** Apnea (see also CLINICAL PHARMACOLOGY), Upper Airway Obstruction, Wheezing, Dyspnea, Hypoventilation, Bronchospasm, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia, Pharyngitis. **Skin and Appendages:** Flushing, Urticaria, Pruritus. **Special Senses:** Amblyopia, Diplopia, Taste Perversion, Eye Pain, Tinnitus. **Urogenital:** Abnormal Urine, Urine Retention, *Green Urine.* **Incidence Less than 1% – Causal Relationship Unknown, derived from clinical trials.** (Adverse events reported in the literature, not seen in clinical trials, are *italicized*.) **Body as a Whole:** *Asthenia.* **Cardiovascular:** Atrial Fibrillation, Bigeminy, Hemmorrhage, Edema, Ventricular Fibrillation, Supraventricular Tachycardia, *Myocardial Ischemia.* **Central Nervous System:** Emotional Lability, Anxiety, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus, Hypotonia, Hallucinations, Neuropathy, Thinking Abnormal.* **Digestive:** Diarrhea. **Hematologic/Lymphatic:** Coagulation Disorder. **Metabolic/ Nutritional:** Hyperkalemia. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Oliguria. In addition to those adverse events listed above, the following adverse event has been reported as a result of postmarketing experience: amorous behavior. **DOSAGE AND ADMINISTRATION:** Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors including preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient. **The following is abbreviated dosage and administration information which is only intended as a general guide in the use of DIPRIVAN Injection. Prior to administering DIPRIVAN Injection, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY – Individualization of Dosage section. In the elderly, debilitated and ASA III or IV patients, rapid bolus doses should not be used in the methods of administration described below. (See WARNINGS.)**

Induction of Anesthesia	Dosage should be individualized and titrated. **Adults***: Most patients require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset). For complete dosage information, see CLINICAL PHARMACOLOGY – Individualization of Dosage.
Maintenance of Anesthesia: Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults***: Most patients require 100 to 200 μg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 50 to 100 μg/kg/min (3 to 6 mg/kg/h).
Maintenance of Anesthesia: Intermittent Bolus	Increments of 25 mg to 50 mg as needed. For complete dosage information, see CLINICAL PHARMACOLOGY – Individualization of Dosage.
Initiation of MAC Sedation	Dosage and rate should be individualized. **Adults***: Slow infusion or slow injection techniques are preferable over rapid bolus administration. Most patients require an infusion of 100 to 150 μg/kg/min (6 to 9 mg/kg/h) or a slow injection of 0.5 mg/kg over 3 to 5 minutes. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require dosages similar to adults, but must be given as a slow infusion or slow injection and not as a rapid bolus. (See WARNINGS.)
Maintenance of MAC Sedation	Dosage and rate should be titrated to clinical effect. **Adults***: A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require a 20% reduction of the adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.) For complete dosage information, see CLINICAL PHARMACOLOGY – Individualization of Dosage.

*Adults – healthy, less than 55 years of age

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through filters with a pore size less than 5 μm because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness.** DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface or vial rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing DIPRIVAN Injection from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only. Any unused portions of DIPRIVAN Injection, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injection.

Shake well before use. Rev B 03/92
Made in Sweden
Manufactured for:

STUART PHARMACEUTICALS A business unit of ICI Americas Inc., Wilmington, DE 19897 USA

Classified Advertising

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701E/L

The Department of Anesthesiology at the University of Texas Medical School in Houston is recruiting faculty at assistant professor, associate professor, and professor levels. Applicants must be board certified or board eligible and able to obtain a Texas medical license. The faculty positions include responsibilities for teaching, supervising and providing patient care, and participation in clinical or laboratory research and administrative functions of the department. The department has significant and expanding responsibilities in the areas of pain management, obstetrical anesthesia, neuroanesthesia, cardiac and vascular anesthesia, and hyperbaric medicine. Interested individuals should send a copy of curriculum vitae and names, addresses, phone numbers, and permission to contact three reference sources. Information should be sent to Jeffrey Katz, MD, Chairman, Department of Anesthesiology, University of Texas Medical School, 6431 Fannin, Houston, TX 77030. The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

873C/H

ILLINOIS: ANESTHESIOLOGIST
To join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approximately 40,000 (35-mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 887D/L.

887D/L

EASTERN PENNSYLVANIA
Hospital needs two board-certified/board-eligible anesthesiologists to join a fee-for-service group in a 225-bed progressive hospital. Applicants must be a PGIV preferrably with pain management, residency rotation. Reply to Box 888D/I.

888D/I

FLORIDA
BE/BC anesthesiologist needed to join busy group practice, serving a fast-growing 130-bed community hospital. Beautiful small Gulfcoast community, no neuro or OH. Send CV to Gulfcoast Anesthesia Specialists, 6630 West Gulf to Lake Highway, Crystal River, FL 32629.

904F/H

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conference, and teaching responsibilities are part of the fellowship experience. Interested individuals should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 83131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

912F/L

PEDIATRIC ANESTHESIOLOGIST
BC/BE to join a private group in growing Pediatric Medical Center in Atlanta, Georgia. No open hearts or transplants. Send CV to Box 916F/H.

916F/H

PAIN FELLOWSHIP, DIVISION OF PAIN MANAGEMENT, DEPARTMENT OF ANESTHESIOLOGY, SUNY HEALTH SCIENCE CENTER AT SYRACUSE
One or two competitive CA-4 positions available. Extensive clinical exposure to acute and chronic pain management, including cancer and pediatric patients. Opportunity for clinical and laboratory research relative to pain management available. Please send curriculum vitae to P. Sebastian Thomas, MD, Director, Pain Treatment Service, SUNY Health Science Center, Syracuse, NY 13210. Equal Opportunity Employer.

917F/H

PEDIATRIC ANESTHESIOLOGIST
The Section of Pediatric Anesthesiology at Arkansas Children's Hospital is seeking an additional faculty member. Candidates should be BC/BE with an approved fellowship in pediatric anesthesiology. Arkansas Children's Hospital is a state-of-the-art facility providing tertiary and primary care to children in six surrounding states. More than 6000 surgical procedures are performed each year. All facets of care are provided including an active acute and chronic pain service. Interested candidates should apply to Raeford E. Brown, Jr, MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

919F/H

CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

HE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology and Critical Care Medicine has immediate faculty positions at the Instructor, Assistant Professor, Associate Professor, and Professor levels for candidates with experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia and critical care medicine. Responsibilities include the teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interests will be provided. It is expected that candidates who apply for CCM positions will have or be eligible for subspecialty certification. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 87131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

913F/L

ANESTHESIOLOGIST
BC/BE. Openings to join group at 500-bed hospital plus busy outpatient center in Erie, Pa. All types of anesthesia including pain management. Beautiful area with year-round recreation. Competitive salary with opportunity for partnership. Send CV to Anesthesia Consultants of Erie, 225 West 25 Street, Suite 408, Erie, PA 16502.

922GH

Immediate opening for a BC/BE anesthesiologist to join six MD anesthesiologists in a fee-for-service practice in a 350-bed hospital in a retirement community in Sun City, Arizona. No OB, open heart, trauma, or pediatrics. Send replies to Box 923GH.

923GH

Texas Tech University Health Sciences Center, Lubbock has faculty positions available for board certified/eligible anesthesiologists with training/experience in subspecialty activities (cardiac anesthesia, critical care, and obstetric). The Department has a tradition of strong support to research activities. Salary is competitive with good benefits. Lubbock is located in the sunbelt within driving distance of the mountains and skiing. It is the home of a major university offering an excellent lifestyle. Equal Opportunity Employer. Please address correspondence, with references and curriculum vitae, to Gabor B. Racz, MD, Chairman, Department of Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

924GH

NORTH EAST, INDIANA
Group seeking BC/BE anesthesiologists to join large MD-only group. All types of anesthesia provided, including OH and OB. Immediate opening. Early partnership offered. Send CV to Box 926G/I.

926G/I

The Department of Anesthesiology at Duke University Medical Center invites qualified full-time faculty to apply for positions in the following categories: NEUROANESTHESIA—We are seeking an academic faculty candidate trained in neurosurgical anesthesia to lead a developing neuroanesthesia section as chief of the section. This opportunity requires a candidate with a primary interest in investigative research and teaching in addition to clinical expertise in all aspects of neuroanesthesiology including an interest in the development of a neurological intensive care unit. A new spacious neuroscience facility at Duke fosters interdisciplinary relationships with neuropharmacology, neuroradiology, neurobiology, and neurology. The neuroscience program at Duke University is one of the five developing centers of excellence at this nationally prominent university. CRITICAL CARE MEDICINE—We are seeking individuals who are ABA certified or board eligible in critical care medicine, for the position of Co-Director, SICU at the Durham VA Medical Center (where a new ICU tower is under construction) and/or as critical care faculty in the SICU at Duke University Medical Center. Faculty will play an essential role in the coordination of care in a multidisciplinary consulting service and in the development of an interdisciplinary Critical Care Fellowship program. GENERAL INTERESTS AND CLINICAL PHARMACOLOGY—We have positions for starting academicians whose subspecialty interests are broad or undefined, but who desire to begin an academic career in a setting with an emphasis on clinical research in pharmacology and epidemiology as it relates to the practice of anesthesiology.

Academic titles and compensation for the above positions will be commensurate with experience and credentials in education, clinical service, and research. Candidates must be board certified or board eligible, and eligible for an unrestricted North Carolina medical license. Please send letter of application and curriculum vitae to J. G. Reves, MD, Box 3094, Duke University Medical Center, Durham, NC 27710. Duke University is an Affirmative Action-Equal Opportunity Employer.

927G/I

LAKE CHAMPLAIN-ADIRONDACK REGION NEW YORK
Growing group seeks a BC/BE anesthesiologist at 410-bed regional referral hospital. Department consists of six anesthesiologists and two CRNAs for 6000 cases/year. No hearts or transplants. Mostly Narkomed 3 machines with H-P Merlin monitors. Plattsburgh is located at the foothills of the Adirondacks and on Lake Champlain, the sixth largest lake in the country. Montreal and Lake Placid region are within 1-hour drive. Excellent public and private schools, state university, affordable real estate, active arts council, and wide variety of recreational activities combine to offer an extraordinary family environment. For details or to view a video of the hospital and community, contact Hannah Hanford, Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

929G/I

CALIFORNIA
University of California, Irvine: Openings for faculty positions in the Department of Anesthesiology. (1) Assistant or associate professor level in the in-residence series. Responsibilities include teaching and research. (2) Clinical instructor and assistant professor level in the clinical series. Responsibilities include teaching and clinical service. Participation in research is highly desirable but not mandatory

Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT
Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

DIRECTOR OF ACUTE AND CHRONIC PAIN SERVICE
UMDNJ, NJ's university of the health sciences, is seeking applicants for the position of Director of Acute and Chronic Pain Service. Applicant must be a board-certified anesthesiologist with a minimum of 2 years' faculty experience in a multidisciplinary pain center. Evidence of interest in

teaching and demonstrated research ability required. The Director will supervise a busy acute and chronic pain service with two fellows and should be familiar with all state-of-the-art pain therapies. Faculty rank and salary commensurate with qualifications.

Contact Sanford L. Klein, DDS, MD, Chairman, Department of Anesthesia, UMDNJ-Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place, CN 19, New Brunswick, NJ 08903-0019. UMDNJ is an Affirmative Action/Equal Employment Opportunity Employer, m/f/h/v, and a member of the University Health System of New Jersey.

932H

TENNESSEE
Expanding department requires additional anesthesiologists. Full-time positions available at levels of instructor to associate professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) meet Tennessee license requirements; (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curriculum vitae, bibliography, and the names and addresses of three references to John Zanella, Jr, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

934H/J

ANESTHESIOLOGIST
Multispecialty group of 43 physicians adjacent to 165-bed hospital in need of BC/BE anesthesiologist. Located in West Texas City of 80,000 with excellent recreational activities. Salary guarantee with bonus based on production. Send CV to West Texas Medical Associates, 3555 Knickerbocker Road, San Angelo, TX 76904.

936H/A

NEW ORLEANS
Louisiana State University Medical Center, Department of Anesthesiology, is seeking a board-certified anesthesiologist who is interested in directing publications and research. Outstanding opportunities for clinical studies are available. No night call, weekends, or holidays are required. Excellent salary and fringe benefits. Eligibility for Louisiana licensure is prerequisite. Please send curriculum vitae to M. Naraghi, MD, Professor and Chairman, LSU Department of Anesthesiology, 1532 Tulane Avenue, New Orleans, LA 70140. LSUMC is an EEO/AA employer.

937H/A

ANESTHESIOLOGIST
The Shriners Hospitals for Crippled Children in Greenville, South Carolina is seeking an additional BC or BE pediatric anesthesiologist. This position offers opportunity for pain management and postoperative critical care patient management. Research resources in conjunction with Clemson University are available. We are a progressive and academically oriented orthopedic hospital with an interesting patient population drawn from six states. This upstate Carolina location provides a pleasant setting in the foothills of the Blue Ridge Mountains, and is within easy drive to coastal recreational areas. Contact Deborah A. Nicholas, MD, Director of Anesthesiology, Shriners Hospitals for Crippled Children, 950 West Faris Road, Greenville, SC 29605.

938H

ANESTHESIOLOGIST TO DEVELOP PAIN PRACTICE
Opportunity: Large anesthesiology group practice desires new associate with interest and experience (1-year fellowship preferred) in chronic pain practice. All subspecialty areas covered. Acute and chronic pain practice growing rapidly. New associate should be able to provide anesthesia care also. Midsize city, Florida, close to water. Great community to raise family. Partnership track. If interested, send curriculum vitae to Box 939H.

939H

OLEAN, N.Y.
Anesthesiologist to join expanding group serving busy hospital in the beautiful Southern Tier. Very competitive salary and benefits. School loans may be forgiven. Send CV to Joseph Kehoe, RR 1, Box 363, Clayton, NY 13624 or call (315) 686-2434 for details.

940H/J

CARDIAC ANESTHESIOLOGIST
Albert Einstein Medical Center is a 600-bed, university-affiliated, tertiary-care hospital with a rapidly growing cardiac surgical program. The Division of Cardiac Anesthesia seeks BC/BE individuals who have completed a cardiac fellowship or have significant cardiac experience. The position includes clinical care and teaching responsibilities. Rank and salary commensurate with experience. Send curriculum vitae to Rick Fine, MD, Chairman, Division of Cardiac Anesthesia, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141-3098.

941HI

ILLINOIS
Opening for full or part-time BC/BE anesthesiologist to join group practice with academic affiliation. Eleven physicians and 15 CRNAs, cardiothoracic, neuro, neonatal, and OB. Excellent salary and benefits. Send CV to Sangamon Anesthesiologists, St. John's Hospital, 800 East Carpenter, Springfield, IL 62769. (217) 544-3311 (collect).

942H/J

ANESTHESIOLOGIST — BC/BE — Immediate opening. All specialties including cardiac. Excellent salary leading to early partnership. Send CV to Medical Associates, PO Box 141, Minot, ND 58702. (701) 857-5448; FAX (701) 839-8024.

943H/J

MASSACHUSETTS
Expanding Anesthesia Department with residency program in university-affiliated teaching hospital, Boston area, seeks two BC/BE anesthesiologists. One with special interest in OB, one with special interest in pain management, to join teaching staff. Please contact Dr. Paul Levesque, Department of Anesthesia, St. Elizabeth's Hospital, 736 Cambridge Street, Boston, MA 02135. Phone: (617) 789-2782.

944H

TEXAS
Private practice group is seeking BE/BC anesthesiologist(s) to join new group forming in North Central Texas just minutes from the Dallas/Ft. Worth Metroplex. Excellent starting salary and practice opportunity. Also accepting applications from CRNAs seeking employment. Facility is a 200-bed community hospital involving predominantly orthopedics, general, and ENT cases with obstetrical service starting immediately. Send CV to NTAA, P.O. Box 630652, Iriving, TX 75063-0652.

945HI

PENNSYLVANIA
The ALBERT EINSTEIN MEDICAL CENTER has two faculty positions available. (1) PAIN: To spend 40% of time in pain clinic and additional time on the acute postoperative pain service. Possibility for appointment as Co-Director of Pain Medicine for the right individual. For the individual with special interest in upper extremity regional blockade, there is an opportunity to work with two new hand surgeons. (2) PEDIATRIC: To become a member of a four-person pediatric anesthesia team. About 20% of time will be pediatrics.

For both positions, clinical responsibility is for all types of predominantly adult cases except cardiac. Interest in teaching residents required; interest in research preferred.

The Albert Einstein Medical Center is a modern 600+ bed tertiary hospital, level one trauma center, and a transplant center

in Philadelphia. Over 12,000 anesthetics performed annually. All faculty (18) receive full academic appointments at the Temple University School of Medicine. Very competitive salary and benefits. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

946HI

MEMORIAL SLOAN-KETTERING CANCER CENTER

Postgraduate Course on "Current Concepts in Cancer and Acute Pain Management," December 10–11, 1992. This course will provide a broad coverage of the management of cancer pain and acute pain for the practicing anesthesiologist. The objective is to exchange information on recent advances, current concepts in diagnosis, and the technical advancement in pain management.

HIGHLIGHTS: State-of-the-art lectures, syllabus, CME credit in Category I.

REGISTRATION: $350.00 for physicians before October 1, 1992; $400.00 for physicians from October 2 to December 9, 1992; $450.00 for ON-SITE registration; $250.00 for 1-day attendance; $200.00 for residents,* fellows,* and nurses (with letter from Program Director*). For more details, please contact: CME office, MSKCC, 1275 York Avenue, New York, NY 10021. (212) 639-6754, (212) 717-3140 FAX.

947HI

PAIN MANAGEMENT TRAINING—ACUTE AND CHRONIC—CA-3 AND FELLOWSHIP POSITIONS

University of Cincinnati Anesthesia Department and the Pain Control Center are seeking applications for Fellowship (preferred) and CA-3 positions in acute and chronic pain management, including cancer pain and pediatric pain management. Chronic benign pain is managed in an interdisciplinary fashion, run by anesthesiologists; program includes inpatient, intensive outpatient, and standard outpatient programs. The Acute Pain Service is aggressive and well accepted, employing all modalities in the management of postoperative and ICU/trauma patients. Opportunities are available for clinical research. Direct inquiries to Donna Benesch, Department of Anesthesia, University of Cincinnati Medical Center, 231 Bethesda Avenue, ML 531, Cincinnati, OH 45267-0531. Phone: (513) 558-6356, FAX: (513) 558-0995.

948H/J

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

949H/L

FELLOWSHIPS

The Department of Anesthesiology at the University of Alabama at Birmingham offers fellowships for 1–2 years with a 50% to 80% commitment to clinical or bench research with the remaining 20% to 50% commitment to clinical training. Fellowships are available without a research commitment. The fellowships are available in the following areas: (1) *Cardiothoracic Anesthesia*, (2) *Pain Management* (including chronic pain, postoperative pain, pain management of patients with terminal cancer), (3) *Transplantation* (including renal, hepatic, pancreatic, cardiac, and lung), (4) *Neuroanesthesia* (including brain and spinal cord electrophysiological monitoring), (5) *Outpatient Anesthesia*, (6) *Obstetrics*, (7) *Laboratory Research* (pain mechanisms, ischemia-reperfusion injury, nitric oxide, and others). Please send curriculum vitae to Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham AL 35233. An Affirmative Action/Equal Employment Opportunity Employer.

950H/J

CHIEF—CRITICAL CARE DIVISION, ASSOCIATE DIRECTOR—SURGICAL ICU

Department of Anesthesiology, University of Alabama at Birmingham is seeking a board-certified anesthesiologist, certified or eligible in critical care medicine, for Chief—Division of Critical Care and Associate Director—Surgical ICU. Responsibilities include subspecialty resident education in critical care, patient care, research, administration, and recruitment of anesthesiologists-intensivists. Excellent research opportunities. Highly competitive salaries. Contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

951H/J

CA-IV POSITIONS IN ANESTHESIOLOGY

The Department of Anesthesia at New England Medical Center Hospitals, Boston, Massachusetts (Tufts University) is accepting applications for CA-IV positions in adult cardiac anesthesia. This will be a 6–12-month rotation specializing in all aspects of cardiac anesthesia. Include CV with letter. Reply to Box 952HI.

952HI

A WEEKEND OF MOCK ORAL EXAMS

Mock orals, not lectures. We are the original course in this format. 20 hours category I CME credit, two board-certified instructors, 12 students maximum. Dallas, August 21–23. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

897H

ORAL EXAM WARM-UPS

Polish your presentation. Take practice exams by phone. PHONEPREP. (419) 843-4480.

909H

DON'T FAIL THE WRITTEN BOARDS!

Unique study program including memory devices, methods for improved retention, guessing techniques, etc. Practice questions with answers, explanations and references, new Keywords. Get MEDTEXT not imitations. Call 1-800-695-6301 for information 24 hours. Call 1-800-232-TEXT for orders. MC/V accepted.

933H/A

PASS YOUR ORAL BOARDS—FOR ONLY $15.00??!!??

New guide gives you valuable tips, hints, and suggestions for one low price. Send $15.00 check or money order, or write for free further information, to Poterack Systems, Department AA, 4422 Shavano Cross, San Antonio, TX 78230.

935HI

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS

The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/H

Dial 1-800/RENT-A-DOC

For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-800/736-8236 * PO Box 640 * Michigan City, IN 46360.

832A/L

ANESTH ANALG
1992;75:A52–6

J. STEPHENS MAYHUGH AND ASSOCIATES, INC. LOCUM TENENS ANESTHESIA SERVICES
Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

755I/H

DANIEL & YEAGER LOCUM TENENS
Daniel & Yeager is the only name you need for locum tenens. Anesthesia is our specialty, so you are assured of our personal attention. Earn a premium income while eliminating administrative headaches and malpractice premiums; we cover it all. Call 1-800-264-1919 or write to 200 Clinton Avenue, NW, Suite 400, Huntsville, AL 35801.

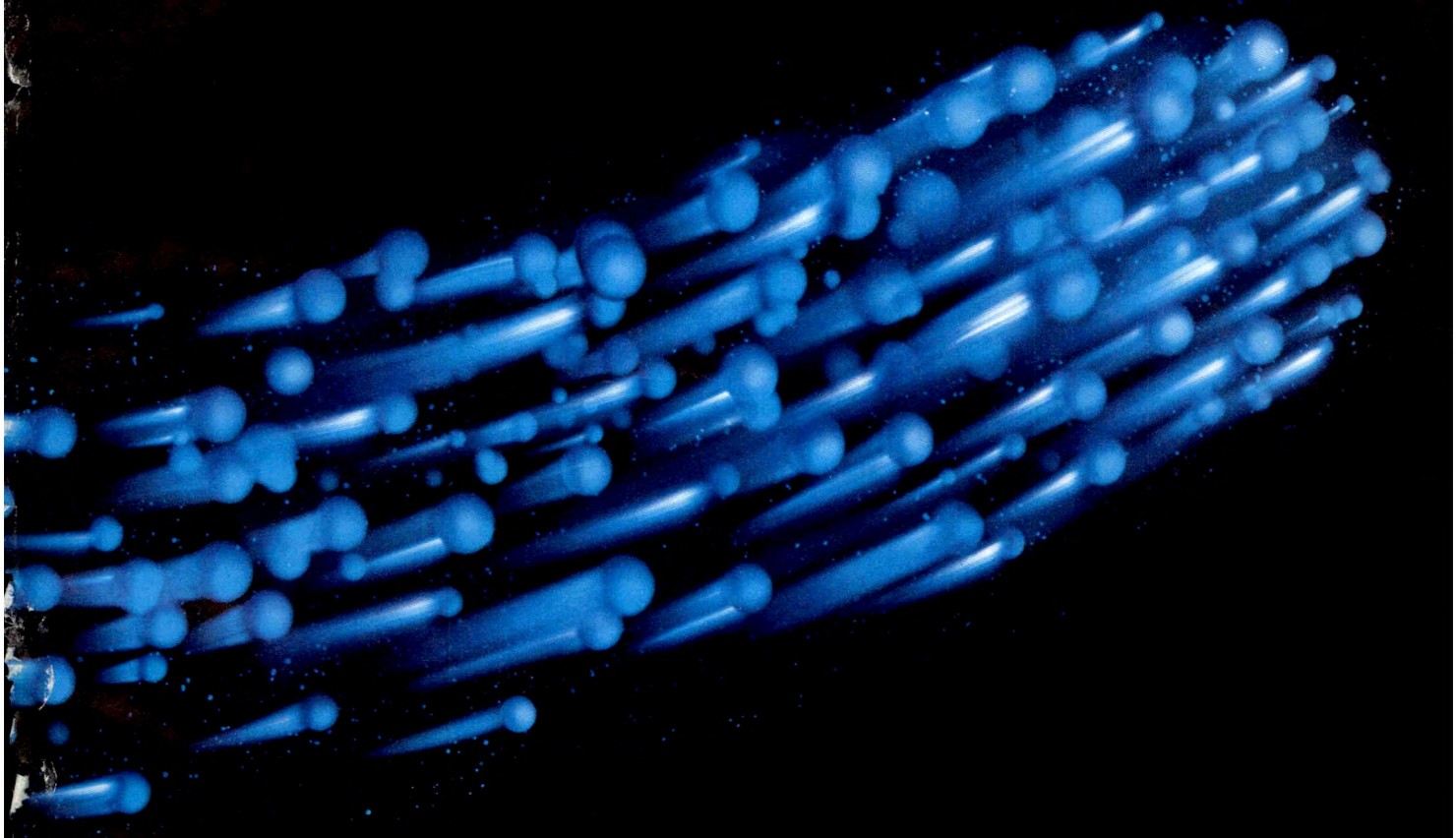
898E/L

---

new

suprane™

desflurane



Coming soon from

Anaquest

A BOC Health Care Company

Critical Care Worldwide

© 1992 Anaquest Inc

The Osler Institute

Anesthesiology Board Review Courses

August 4-9, 1992 – Chicago

†September 14-19 – Boston

Now, special programs for written and oral boards

OBJECTIVES

- Improve basic and clinical knowledge of anesthesiology
- Assist residents and fellows to better organize for further study
- Prepare candidates to take their written and oral exams

METHODS

- HOME STUDY questions, answers, assignments and keywords
- SEMINAR with projection slides and lecture-note syllabus
- PRACTICE EXAMS for written and oral board exams

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities, but from people who are relatively unknown as well."**

Physiology

Respiratory Physiology
Cardiovascular Physiology
Neurophysiology
Hepatic & Renal Physiology
Acid-Base and Blood Gas

Pharmacology

Pharmacokinetics
Inhalation Anesthetics
Intravenous Anesthetics
Local Anesthetics
Muscle Relaxants
Central Nervous Drugs
Cardiac & Diuretic Drugs
Interactions & Genetics

Physical Sciences

Applied Anatomy
Physics and Gas Laws
Anesthesia Machines
Breathing Systems

Fundamentals

Preop. Evaluation & Prep.
Patient Monitoring
Airway Management
Fluid and Blood Therapy
Cardiopulmonary Disease
Hepatic & Renal Disease
Metabolic Disease
Recovery Room

Regional Anesthesia

Autonomic Blocks
Spinal and Epidural Blocks
Upper Extremity Blocks
Lower Extremity Blocks
Chronic Pain Management

Specialty Areas

Obstetric Anesthesia
Pediatric Anesthesia
Cardiac Anesthesia
Thoracic Anesthesia
Neuroanesthesia
Ophthalmic & E.N.T.
Geriatric and Outpatients

Faculty

Hassan Ali, M.D.
Harvard University
Solomon Aronson, M.D.
University of Chicago
Jonathan Benumof, M.D.
Univ. of California, San Diego
Edward Brian, M.D.
University of Arkansas
Eugene Y. Cheng, M.D.
Medical College of Wisconsin
Edward Czinn, M.D.
Univ. of Illinois, Chicago
Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville
Boleslaus A. Falinski, M.D.
Emory University
Elizabeth Frost, M.D.
Albert Einstein College of Med.
Christopher Gallagher, M.D.
Anesthesia Service, San Diego
Harold Heyman, M.D.
University of Illinois
Lewis Hodgins, M.D.
Duke University
Anthony D. Ivankovitch, M.D.
Rush Medical College
Niels Jensen, M.D.
University of Iowa
Charles Levine, M.D.
York Hospital, York, PA
Eugene Lipov, M.D.
Rush Medical College
David Lubarsky, M.D.
Duke University
William Martin, M.D.D.O.
Med. Univ. of South Carolina
Michael Newman, M.D.
Rush Medical College
Peter Pan, M.D.
Medical College of Virginia
David Rothenberg, M.D.
Rush Medical College
Ramez Salem. M.D.
University Of Illinois
Astride Seifen, M.D.
University of Arkansas
Daniel Siker, M.D.
Medical College of Wisconsin
Theodore C. Smith, M.D.
Loyola University of Chicago

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name _____

Address _____

City/State _____

Zip _____ Phone _____

Mail today to:

1094 East Dawn Drive, Dept. A208A
P.O. Box 2218
Terre Haute, IN 47802

☐ August 1-3, 1992 – Los Angeles
☐ August 4-9, 1992 – Chicago
☐ August 14-16, 1992 – Atlanta
☐ September 14-19, 1992 – Boston
☐ Check enclosed for $ _____
☐ Please send **FREE SAMPLE**

Written Board Review

Lectures and written exam seminars

- Home-study keywords with discussions and questions with answers.
- Six-day lectures with syllabus.
- **Seminars for written exam questions.**
- September 14-19.

Oral Board Review

Mock oral exams and lectures

- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Six-day lectures with syllabus and concurrent mock oral exams most hours.
- **Registration includes one mock oral.**
- Extra public mock oral exam ($80), private mock oral exam ($110).
- August 4-9; September 14-19.

Oral Board Tutorial Days

Choose any days – groups limited to 24

- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Mock oral exams in groups **limited to 24.**
- **Includes one public mock oral per day.**
- Extra public mock oral exams ($80), private mock oral exams ($110).
- August 4-9; September 14-22.

Two-Part Board Review

Nine mock orals in any two courses

- Any course in 1992, plus any other within three years. One course may be up to six Oral Board Tutorial days of your choice.
- Choose between lectures and concurrent mock orals or written exam discussions.
- **Nine (9) mock oral exams in groups limited to 24 participants.**

Unconditional Guarantee

- If you fail the next Anesthesiology Board Exam you take after taking one of these courses, we will refund half of your last course registration fee and allow you to repeat the course once for FREE.
- This is NOT conditional upon you taking more than one course, or extra mock orals.
- Last year, after we first made this guarantee, **less than 2% requested a refund.**

Information

The Osler Institute
1094 East Dawn Drive, P.O. Box 2218
Terre Haute, IN, 47802
(800) 356-7537

†Plus mock orals only September 20-22.

* *Comments by past Osler participants*

Alfenta®
(alfentanil HCl) Injection

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

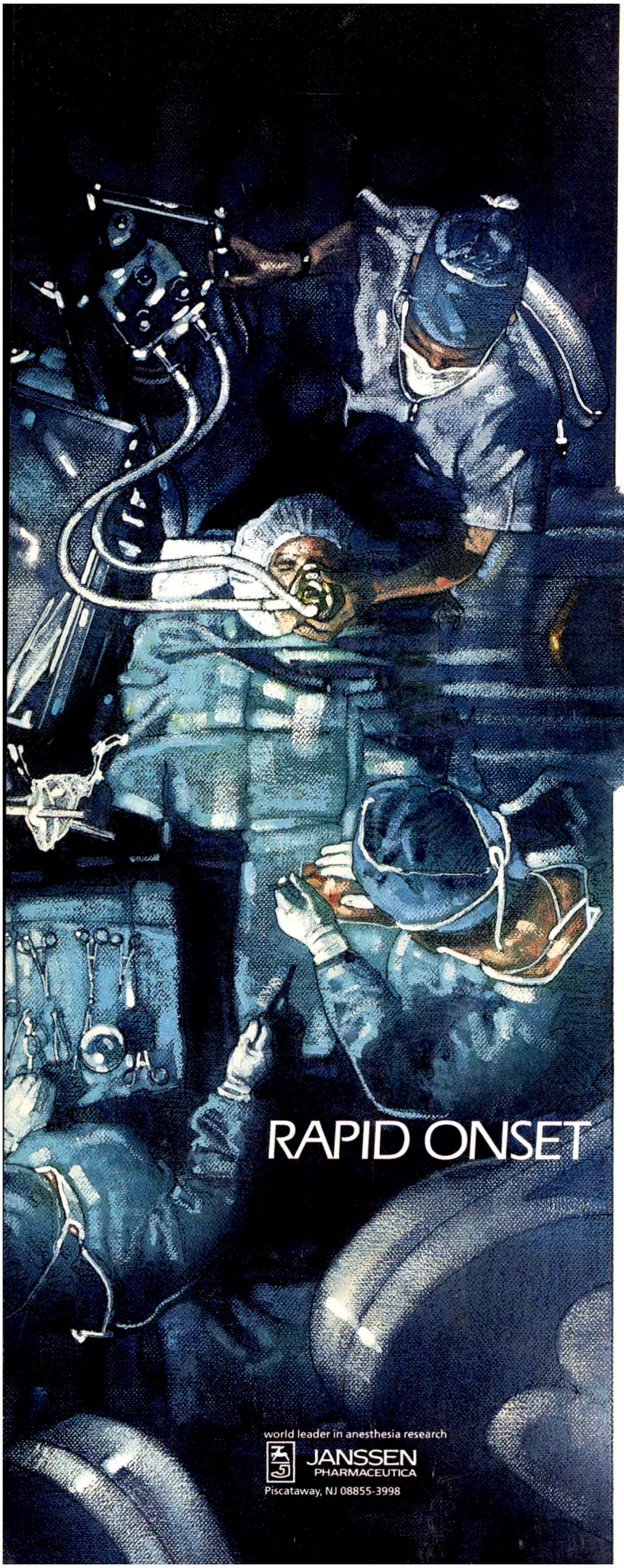
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

JANSSEN PHARMACEUTICA
Piscataway, NJ 08855-3998

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

© Janssen Pharmaceutica Inc. 1992



MEETING THE DEMANDS OF TODAY'S AMBULATORY SURGERY

RAPID RECOVER™

Alfenta®
(alfentanil HCl) Injection CII

world leader in anesthesia research

JANSSEN PHARMACEUTICA
Piscataway, NJ 08855-3998

Please see following page for brief summary of Prescribing Information.